2.5 Clinical Overview

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AE	Adverse events
ASD	Autism spectrum disorders
AUC	Plasma concentration-time curve
Bio	Bioavailability
BL	Bright light
BW	Body weight
CI	Confidence interval
Cl	Clearance
Cl/F	Clearance (oral)
Cmax	The highest concentration of a drug in the blood, cerebrospinal fluid, or target organ after a dose is given
CYP1A1 / CYP1A2 / CYP2C19 / CYP1B1	Cytochrome P450 enzyme(s)
d	Day(s)
DL	Dim light
DLMO	Dim light melatonin onset
D/N	Day time/Nighttime activity ratio
DSWPD	Delayed sleep wake phase disorder
ECT	Electroconvulsive therapy
EMA	European Medicines Agency
F	Female(s)
g	Gram(s)
h	Hour(s)
HV	Healthy volunteer
IV	Intravenous
kg	Kilogram(s)
L	Litre(s)
L5onset	The least active 5-hour period (24-hour distribution activity)
LSEQ	Leeds Sleep Evaluation Questionnaire
M	Male(s)
M	Melatonin
M10onset	The start of the most active 10-hour period (24-hour distribution activity)
MDD	Manic depressive disorder
MEL	Melatonin
mg	Milligram(s)

µg	Microgram(s)
min	Minute(s)
ml	Millilitre(s)
MLT	Melatonin
mol	Mole(s)
MT	Melatonin receptor sites
n	Number (of)
NA	Not applicable
NC	Not calculated
nmol	Nanomole(s)
NNT	Number needed to treat
NR	Not reported
NS	Not significant
OC	Oral contraceptives
p / PLA / PLB	Placebo
pg	Picogram(s)
PK	Pharmacokinetic
POMS	Profile Of Mood
PRM	Prolonged release melatonin
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index'
RA	Relative amplitude (ratio of M10-L5/M10 + L5)
RSBD	Rapid eye movement sleep behaviour disorder
RCT	Randomised clinical trial
REM	Rapid eye movement
RR	Regular release
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SE	Sleep efficiency
SEI	Sleep efficiency index
SL	Sleep latency
SO	Sleep onset
SOL	Sleep onset latency
SR	Sustained release
SSR	Surge-sustained release
SSS	Stanford Sleepiness Scale
TOA	Time of administration
T½	Half-life

Tmax	Time to maximal plasma/serum concentration
TST	Total sleep time
TZE	Time zones east
TZW	Time zones west
VAS	Visual analogue scale
V_D	Volume of distribution
V_D/F	Volume of distribution (oral)
w	Week(s)
WASO	Wake after sleep onset
Yrs	Year(s)

1. PRODUCT DEVELOPMENT RATIONALE

Ceyesto 1 mg/ml Oral Solution is an oral solution containing 1 mg melatonin per ml solution in 100 ml, 150 ml or 200 ml amber glass bottles. The active substance, melatonin is an established product, widely used worldwide for the induction of sleep. This Clinical Summary supports an Application for Marketing Authorisation according to Regulation 54 (equivalent to Article 10a of Directive 2001/83/EC) considered as a bibliographic (well-established use) application.

In this bibliographic application, the Applicant is requesting the following indications:

Ceyesto 1 mg/ml Oral Solution is indicated for:

(i) Delayed sleep wake phase disorder (DSWPD) in children and adolescents aged 6-17 years and adults up to 25 years of age, where sleep hygiene measures have been insufficient.

(ii) Short-term treatment of jet lag in adults.

(iii) Insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

(iv) Single use for short-term sedation under medical supervision to facilitate electroencephalograms (EEG) in children and adolescents from 1 to 18 years of age.

To support this application, the Applicant presents:

- The results of literature searches supporting the established pharmacokinetic (PK), pharmacodynamic (PD), efficacy and safety profile of melatonin in these indications and populations with tabulations of data for the pivotal and supportive studies in each indication in Module 2.7.3 and safety data in Module 2.7.4.
- Documentation of well-established use (WEU) in the United Kingdom (UK), with particular emphasis on clinical practice within the National Health Service (NHS) summarised in Module 2.7.3.4.
- The licence history of Melatonin products in the UK and European Union (EU) in Section 1.2.
- A review of available prescription data and postmarketing safety data in Module 2.7.4.

1.1 Clinical Background

Sleep disorders are a group of conditions that affect the sleep-wake circadian rhythm, leading to social and professional consequences, and negative impacts on general health. Sleep is fundamental to a person's emotional and physical health. Inadequate sleep is a known risk factor for obesity, diabetes, heart disease and depression. Sleep disorders create a significant burden on the health care system. The average annual medical expense of an individual with a chronic sleep disorder is $2000 more than someone without a sleep disorder. Insomnia has economic impacts aside from the medical costs such as reduced productivity and increased absenteeism [redacted]. Sleep disorders are a broad category of disorders that encompass all types of dysfunctions involving sleep, including difficulty falling asleep at night, poor sleep quality, early waking, circadian rhythm disorders, parasomnias, sleep-related movement disorders and sleep-related breathing disorders. The consequence of sleep disorders is often daytime fatigue. People who have sleep disturbances report impaired cognition with an impaired ability to fulfil daily tasks involving memory, learning, logical reasoning and

mathematical operations. These effects have been confirmed in numerous objective studies [redacted]

The main classes of drugs commonly used for the treatment of insomnia in adults and children where behavioural interventions are ineffective are, benzodiazepines, benzodiazepine agonists, antidepressants, and anxiolytics with barbiturates rarely used in current clinical practice. These drugs can cause a large number of side effects associated with excessive daytime sleepiness, decreased concentration, and impaired attention switching and can cause deterioration of short-term memory. In some cases, with prolonged use of these drugs, dependence may form, and with discontinuation, a "rebound phenomenon" may occur. Similar classes of drugs can be used as sedatives although the potential side-effects, particularly respiratory depression, and the requirements for careful monitoring are a concern.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland during the dark phase of the light/dark cycle, has daily and seasonal rhythms which respond to the annual changes in photoperiod and lead to adaptive alterations of the physiological state. Endogenous melatonin from the pineal gland is rapidly delivered to the body via the systemic circulation, but melatonin is also synthesized in other structures such as the retina, Harderian gland, gut and epidermis where it may play an auto/paracrine role.

Melatonin secretion and plasma melatonin levels increase shortly after the onset of darkness, peak around the middle of the night and decline to the daytime low by dawn. Peak melatonin secretion is almost diametrically opposite the peak daylight intensity, with daylight being the main stimulus maintaining the circadian rhythmicity of melatonin secretion.

The intent of treatment with Ceyesto, as an immediate release melatonin formulation, is to target sleep processes within the first few hours after administration. The primary targets are correction of any misalignment of the circadian rhythm (chronobiotic effect) and support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect). These effects are similar across all sleep disorders and populations.

The chronobiotic effect of melatonin to reset the circadian rhythm is driven by increasing the melatonin level up to 7 hours before the endogenous dim light melatonin onset (DLMO). This is the most important component of efficacy in DSWPD and jet lag. The chronobiotic effect also contributes to the effect of melatonin in sleep onset insomnias with a delayed DLMO. A change in DLMO therefore provides a robust objective marker of efficacy in patients where DLMO is misaligned at baseline.

The hypnotic effect of immediate release melatonin peaks swiftly after administration, closely following plasma levels. Melatonin is intended to improve the patient's ability to fall asleep with the time of sleep onset, and the sleep onset latency, considered the key clinical parameters. The subtypes of insomnia where immediate release melatonin is expected to be particularly effective are those which include difficulty or delay in initiating sleep. During the early hours of the night, sleep maintenance and sleep quality may also be improved, but this is difficult to measure independently from the total sleep experience across the night. Total sleep time may also be improved where it was impacted by the difficulty falling asleep. In general, patients receiving immediate release melatonin would be expected to awake at the same time or earlier, as they may have completed their natural sleep cycle earlier. Immediate release melatonin is not expected to have any effect to prolong sleep during the early morning hours and patients where the predominant complaint includes waking in the early hours of the morning are not expected to benefit from immediate release melatonin. However, it should be noted that in patients with

impaired clearance of melatonin such as some elderly patients, higher levels, and hence improvement of sleep, may persist throughout the night. The hypnotic effect of melatonin is the main effect in the induction of sedation.

Melatonin was first discovered in 1958 and the circadian rhythm of melatonin production was demonstrated in 1975. Since then, it has been investigated as a potential treatment for insomnia and in a number of neurological and other conditions. Reports of administration of exogenous melatonin date back as far as 1969 [redacted], with the effects of melatonin on sleep and behaviour studied from the 1970s [redacted], and involvement in jet lag noted from the 1980s [redacted]. The therapeutic use of melatonin was also proposed in the 1980s [redacted] with daily doses up to 240 mg being studied [redacted]. In the UK until 1995 when the MHRA (MCA) classified it as a medicinal product, melatonin was registered as a health supplement and available for use as a sleeping aid [redacted] In Europe melatonin is widely available as both a medicinal product and as a herbal or dietary supplement; in France and Latvia dietary supplements containing up to 2mg are permitted while in Spain, Italy, Greece and Poland among others up to 1mg is allowed in dietary supplements whilst in Germany just 0.28mg are allowed in dietary supplements and in e.g. the UK, Denmark and Switzerland it is not permitted at all in dietary supplements [redacted]. In the US it is available as a food supplement at doses from 0.3 to 10mg. Further, since 2012 the European Food Standards Agency has allowed two claims relating to the presence of melatonin in foodstuffs (Commission Regulation (EU) No 432/2012): "Melatonin contributes to the alleviation of subjective feelings of jet lag" and "Melatonin contributes to the reduction of time taken to fall asleep". The second of these claims is considered to form the vast majority of the use of supplements across Europe below 2mg. Both applications of use for these claims are considered to fall under the Applicants submitted indications.

The first approvals for melatonin in the EU as a medicinal product were in Poland and Hungary in 2001 and 2003 respectively followed by the EU wide approval of Circadin in 2007 and further multiple approvals. Overall, melatonin has been in safe and effective use for the requested indications for well over 10 years as described in Module 2.7.3 and Module 2.7.4. A significant degree of off-label use is prevalent with melatonin as shown by the prescribing data and clinical guidelines described in Module 2.7.3. The Applicant's submission is clinically justified and approval will provide an improvement in prescribing and patient safety. The extent of use on a geographical basis for over 10 years fulfils the requirements of Article 10(1)(a)(ii) of Directive 2001/83/EC. The submitted package of bibliographic data is considered sufficient to conclude that there is a high level of scientific interest, and that melatonin is effective in the proposed indications.

The definitions of chronic insomnia in guidance such as ICD-11, DSM-V, and ICSD-3 comprise a predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:

1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
3. Early-morning awakening with inability to return to sleep.

The EMA 'Guideline on medicinal products for the treatment of insomnia' (EMA/CHMP/16274/2009 Rev. 1, February 2011) also includes a feeling of non-restorative sleep, although this subjective classification relies solely on patient reported outcomes.

In general, the sleep disorder should have been present for at least 3 months for at least 3 nights per week despite adequate opportunity for sleep and cause problems in daytime functioning.

In clinical practice many patients have mixed insomnia with differing mixtures of these symptoms. Further, patients with sleep onset insomnia may also have a delay in DLMO which contributes to the overall insomnia symptoms. The subtype of chronic insomnia in the individual patient is an important factor in determining a treatment pathway. Immediate release melatonin is a well-established treatment to support sleep onset, and normalises circadian rhythm in patients with difficulty or delay in initiating sleep.

Delayed sleep wake phase Disorder (DSWPD)

Delayed sleep phase syndrome (DSPS) or Delayed Sleep Wake Phase Disorder (DSWPD) as defined by the (i) International classification of diseases (ICD-11, 2019); (ii) Diagnostic and statistical manual of mental disorders (DSM-V, 2013) and (iii) International classification of sleep disorders (ICSD-3, 2014) as a disorder in which a person's sleep is delayed by two hours or more beyond what is considered an acceptable or conventional bedtime. The delayed sleep then causes difficulty in being able to wake up at the desired time, but other aspects of sleep, such as arousals, quality of sleep, and sleep architecture are not significantly changed [redacted] which is why these parameters are not generally required in the diagnostic process. The underlying sleep disturbance is a misalignment of the circadian rhythm. In DSWPD the baseline DLMO is expected to be at least 2 hours delayed compared to environmental time, although there are no other direct disturbances of sleep or sleep architecture.

DSWPD is highest in adolescents and young adults, with rates estimated between 3.3 and 4.6 percent [redacted]. The prevalence of DSWPD in older adults is much lower, with estimates between 0.2 to 1.7 percent [redacted]. The natural history of DSWPD is such that it typically emerges in late childhood or during adolescence, and without treatment it may be a chronic condition that persists into adulthood (AASM ISCD- 3 2014). The Applicant has considered this in its proposed posology for Ceyesto 1mg/ml Oral solution recommending initiation up to the age of 25 years (i.e. into young adulthood) and continuation of therapy into later adulthood where clinically appropriate.

Although minor differences in terminology remain (DSP-Type in DSM-V and DSWPD in ICSD-3 and ICD-11), the diagnostic criteria are now harmonised between the classification systems (harmonisation initiated in 2010), which were previously very different in their approach to classification and description of circadian rhythm sleep disorders. This is why some publications describe the disorder by its diagnostic characteristics (i.e. chronic sleep onset insomnia with circadian misalignment) rather than as DSPS or DSWPD.

In the treatment of DSWPD melatonin treatment has 2 separate actions, a chronobiotic and a hypnotic effect [redacted]). These two effects can be complementary or conflicting, depending upon the time of administration and the residual serum levels in the early morning hours. The primary intent of treatment of DSWPD with Ceyesto is to correct the misalignment of the circadian rhythm.. The clinical correlate is the sleep time in patients who choose their own bedtime or the sleep onset latency in those with a fixed bedtime.

The secondary effect of Ceyesto in DSWPD is enacted through support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect).

Insomnia in Attention Deficit Hyperactivity Disorder (ADHD).

Attention deficit hyperactivity disorder (ADHD) by definition is characterized by attention disorders, impulsive behaviour, and hyperactivity. Chronic insomnia is a common comorbidity of ADHD. It can be difficult to elicit from children the precise sleep complaint they experience. Difficulties in sleep onset are a robust measure of one subset of chronic insomnia and are a key component of the target of Ceyesto action in chronic insomnia. Approximately one third of medication-free children with ADHD experience chronic sleep-onset insomnia (SOI). This persistent disability to fall asleep at the desired time in the evening may exacerbate daytime mood, behavioural, and/or cognitive problems [redacted]). Medication-free children with ADHD and SOI have a delayed evening increase in endogenous melatonin levels [redacted] and in children without ADHD this phase delay predicted a stronger sleep phase-normalizing effect of exogenous melatonin [redacted] Hence, the Applicant has targeted an indication specifically for insomnia in children and adolescents with ADHD aligned to that already registered in the UK and across Europe. Similarly to patients with DSWPD, ADHD patients whose symptomatic disease continues into adult may continue to benefit from melatonin treatment. The intent of treatment with Ceyesto, as an immediate release melatonin formulation, is to target sleep processes within the first few hours after administration. The primary targets are correction of any misalignment of the circadian rhythm (chronobiotic effect) and support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect). These effects are similar across all sleep disorders and populations.

Single Use for short-term Sedation under Medical Supervision to Facilitate electroencephalograms (EEG) in children and adolescents from 1 to 18 years of age

Initiation of a sedative effect is required for certain medical procedures and tests, particularly in younger patients who might otherwise be unable to keep still to allow satisfactory completion of the procedure, or would be subject to unnecessary anxiety.

Jet Lag

Jet lag is a common complaint of travellers who fly across a number of time zones. The symptoms of jet lag include reduced alertness, daytime fatigue, loss of appetite, reduced cognitive skills, and disruption of the sleep/wake cycle. In susceptible air travel passengers, jet lag may exacerbate affective illness and result in psychiatric morbidity. Dysregulation of circadian rhythms and melatonin secretion represent the common underlying factor in jet lag and other circadian disorders [redacted] Jet lag is caused by desynchronization between the body's circadian system and the new day-night cycle at the traveller's destination. The sleep loss caused by the travel itself often exacerbates jet lag. After a flight through six or more time zones most travellers will take 4-6 days to re-establish a normal sleeping pattern and not feel tired during the day. The severity of jet lag symptoms largely depends on the number of time zones crossed and the direction of travel. They are worse the greater the number of zones crossed. Eastward travel causes more disruption, as it is easier to lengthen than to shorten the natural circadian cycle ([redacted] .

1.2 Current Therapeutic Options

Melatonin is available in the UK in liquid, immediate release tablet and prolonged release tablet formulations, with limited and varying indications and dosage forms available (Table 1). Liquid preparations enable infinite tailoring of dose which is critical to the safe and effective use of melatonin in the paediatric population and allow clinicians to use the 'minimum effective dose'.

The availability of appropriately licensed liquid formulations also avoids the need for crushing of solid dose forms and where administration via a feeding tube is necessary a better option without requiring any extemporaneous preparation. The ability to tailor dosage to this degree and utilise a ready made liquid formulation is not possible when prescribing solid dose formulations.

Various other pharmacological agents have been introduced for various types of sleep disorders in recent decades. Many of these medications are also used as a short-term sedative. Current medications include chloral hydrate, barbiturates, benzodiazepine, benzodiazepine agonists, modafinil, antidepressants, anxiolytics and most recently orexin receptor antagonists. However, these medications may not yet have an established safety profile, may be used outside their intended license indications an also have substantial side effects, including excessive daytime sleepiness, poor tolerance to the medication, cognitive impairment, dependency, and withdrawal. Melatonin is widely used in these indications as a pharmaceutical approach with less side effects [redacted]).

Table 1 Current Melatonin Presentations Licensed in the UK and EU

Name	MAH	Dosage Form	Strength	Country / RMS	Submission Route	CMS	Approval	Legal Basis	Indications
Melatonina LEK-AM	Przedsiębiorstwo Farmaceutyczne LEK-AM Sp. z o.o.	Tablets	1, 3 & 5mg	PL	National	N/A	2001	Not known	As an adjuvant in the treatment of sleep-wake rhythm disorders, e.g. related to the change of time zones or in connection with shift work. The drug also helps to regulate disturbances in the circadian rhythm of sleep and wake in blind patients.
Bio-Melatonin	Pharmyn ApS	Film-coated Tablets	3mg	HU	National	N/A	2003	Article 10a	For the relief of sleep disturbances resulting from an upset of the biological sleep-wake rhythm, such as jet-lags and multi-shift workers, who are 18 years of age or older.
Circadin	RAD Neurim Pharmaceuticals EEC SARL	Prolonged-Release Tablets	2mg	CP	CP	CP	2007	Article 8(3)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Melabiorytm	Aflofarm Farmacja Polska Sp. z o.o.	Tablets	5mg	PL	National	N/A	2016	Not known	As an adjunct in sleep disorders related to changing time zones or in connection with shift work and facilitating rhythm regulation daily sleep and wakefulness in blind patients.
Melatonin Pharma Nord	Pharma Nord ApS	Tablets	3mg	NL	DCP	BE, EE, HU, IE, LT, LV, PL, PT, ES, UK	2018	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Vitalbalans	Vitalbalans	Tablets	3 & 5mg	EE	DCP	CZ, LT, LV, SK, SI	2018	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Oral Solution	Colonis Pharma Ltd	Oral Solution	1mg/ml	UK	National	N/A	2019	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin MMC	MMC	Tablets	3 & 5mg	PL	DCP	DK, SE	2019	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Orifarm	Orifarm Generics	Tablets	3mg	DK	DCP	NO, SE	2019	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Clinigen	Clinigen Healthcare BV	Film-coated Tablets	3mg	NL	DCP	UK	2019	Article 10(1)	For short-term treatment of jet-lag in adults.
Davitamon Melatonine	Omega Pharma Nederland B.V.	Tablets	1,3 & 5mg	NL	National	N/A	2019	Not known	For short-term treatment of jet-lag in adults.
Melatonine DMB	TioFarma B.V.	Tablets	1,3 & 5mg	NL	National	N/A	2019	Article 10a	For short-term treatment of jet-lag in adults.

Name	MAH	Dosage Form	Strength	Country / RMS	Submission Route	CMS	Approval	Legal Basis	Indications
Melatonine Tiopharma									
Melatan	Evolan Pharma AB	Tablets	3 & 5mg	SE	National	N/A	2019	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Capsules	Colonis Pharma Ltd	Capsules	2, 3 & 5mg	UK	National	N/A	2020	Article 10(1) and 10(3)	For short-term treatment of jet-lag in adults.
Melatonin Tablets	Arriello sro	Film-coated Tablets	3mg	UK	National	N/A	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin AGB Tablets	AGB Pharma	Tablets	1, 2, 3, 4 & 5mg	SE	DCP	DK, NO, UK	2020	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Ceyesto	Alturix	Tablets	3mg	FI	DCP	UK	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Unimedic	Unimedic Pharma AB	Oral Solution	1mg/ml	SE	DCP	DK, FI, NO	2020	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Melatonin Alternova	Alternova A/S	Tablets	2mg	DK	DCP	NO, SE	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonine Owlpharma	Owlpharma	Tablets	2mg	NL	DCP	DK, NO, SE	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Noxarem	Vemedia Manufacturing B.V.	Tablets	3 & 5mg	FI	DCP	BE, FR, IT, LU, PT	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonine Valdispert	Vemedia Manufacturing B.V.	Tablets	3 & 5mg	FI	DCP	NL	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonine Sleepzz	Vemedia Manufacturing B.V.	Tablets	3 & 5mg	FI	DCP	NL	2020	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Orifarm Mellaras	Orifarm Generics	Oral Solution	1mg/ml	SE	National	N/A	2020	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

Name	MAH	Dosage Form	Strength	Country / RMS	Submission Route	CMS	Approval	Legal Basis	Indications
Melatonina Polfarmex	Polfarmex S.A.	Tablets	5mg	PL	Natioual	N/A	2020	Not known	As an adjunct in disturbances of the sleep-wake rhythm related to the change of time zones or resulting from shift work and facilitating regulating the circadian rhythm of sleep and wakefulness in blind patients.
Mellozan	EQL Pharma AB	Tablets	0.5, 1, 2, 3, 4 & 5mg	SE	Natioual	N/A	2021	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Melatonin Billev	Billev Pharma ApS	Tablets	0.5, 1, 2, 3, 4 & 5mg	DK	DCP	NO	2021	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Aritonin	YES Pharmaceutical Development Services GmbH	Film-coated Tablets	2 & 3mg	SE	Natioual	N/A	2021	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Melatonin TEVA	TEVA	Prolonged-Release Tablets	2mg	UK	DCP	NO, PT, IS	2018	Article 10(1)	For the short-term treatment of primary insomnia characterised by poo quality of sleep in patients who are aged 55 or over.
Mecastrin	Orifarm Generics	Prolonged-Release Tablets	2mg	DK	DCP	FI, NO, SE	2018	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Melatonin PR Tablets	Generic Partners UK Ltd	Prolonged-Release Tablets	2mg	ES	DCP	PL, UK	2018	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Sloremina	Sigillata Limited	Prolonged-Release Tablets	2mg	IS	DCP	IT	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Lestinora	Sigillata Limited	Prolonged-Release Tablets	2mg	IS	DCP	DE	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Contovera	Sigillata Limited	Prolonged-Release Tablets	2mg	IS	DCP	DE	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

Name	MAH	Dosage Form	Strength	Country / RMS	Submission Route	CMS	Approval	Legal Basis	Indications
Orlome	Sigillata Limited	Prolonged-Release Tablets	2mg	IS	DCP	IT	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Melodia	Ecupharma SRL	Prolonged-Release Tablets	2mg	IS	DCP	IT	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Melatonin Neuraxpharm	Neuraxpharm Arzneimittel GmbH	Prolonged-Release Tablets	2mg	IS	DCP	DE	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Melatonina Generis	Generis Farmaceutica SA	Prolonged-Release Tablets	2mg	PT	DCP	BE, DE, ES, FR, IT	2021	Article 10(1)	For the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.
Slenyto	RAD Neurim Pharmaceuticals EEC SARL	Prolonged-Release Tablets	1 & 5mg	CP	CP	CP	2018	Article 8(3)	insomnia (difficulty sleeping) in children and adolescents (2 to 18 years old) who have: autism spectrum disorder (ASD), a range of conditions that affects the patient's social interactions; Smith-Magenis syndrome, a condition that can lead to learning difficulties.
Voquily	Clinigen Healthcare B.V.	Oral Solution	1mg/ml	SE	DCP	AT, BE, DE, ES, FR, HU, IE, IT, NL, PL	2022	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Orimelan	Orion Corporation	Tablets	3 & 5mg	FI	DCP	DK, NO, SE	2022	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Memita	Orion Corporation	Tablets	3 & 5mg	FI	DCP	DK, NO, SE	2022	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
Melatonine Omega Pharma	Omega Pharma Nederland B.V.	Tablets	3 & 5mg	NL	DCP	ES	2022	Article 10a	For short-term treatment of jet-lag in adults.
Melatonin Evolan	Evolan Pharma AB	Oral Solution	1mg/ml	SE	Natioual	N/A	2022	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17

Name	MAH	Dosage Form	Strength	Country / RMS	Submission Route	CMS	Approval	Legal Basis	Indications
									years with ADHD, where sleep hygiene measures have been insufficient.
Melatonin 3mg Tablets	Pharma Nord ApS	Tablets	3mg	UK	National	N/A	2022	Article 10c	For short-term treatment of jet-lag in adults.
Melatonin Consilient Health 1 mg/ml oral solution	Consilient Health Ltd.	Oral Solution	1mg/ml	UK	MRDCRP	N/A	2022	Article 10a	For short-term treatment of jet-lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

1.3 Placement of Ceyesto 1 mg/ml Oral Solution

Current treatment options for melatonin in various indications are limited by a lack of flexibility in dosing, the lack of an immediate release formulation (IRF), the absence of a liquid formulation and limitations of the license. The use of melatonin in sleep disorders should be as part of a defined treatment pathway, after lack of substantial improvement from non-pharmacologic interventions (Figure 1)

Dosing: The treatment of intrinsic circadian rhythm disorders usually requires lower doses than can be reliably obtained with the current available medication. The advantage of a liquid formulation is that it allows for precise dosing and for lower doses to be used. Conversely, in sedation and jet lag, larger doses are more effective and this becomes inconvenient and expensive if these larger doses are only obtainable by taking multiple tablets.

Immediate release formulation: An IRF is more appropriate for the treatment of circadian rhythm disorders, or mixed disorders that include circadian misalignment, than slow-release formulations as slow release tablets may raise melatonin levels in both the advance and the delay portions of the melatonin phase response curve, thereby reducing their phase shifting action. Immediate release formulations take advantage of the melatonin's short half-life to ensure that the melatonin levels are only raised in the appropriate portion of the phase response curve. This makes it more effective and reduces the likelihood of residual, unwanted sedation the next day. These properties are also ideal for use as a short-term sedative.

Liquid formulation: In addition to accurate dosing, liquid preparations are more acceptable to many patients than tablets. This is particularly the case where there are difficulties swallowing.

License: The current melatonin licenses (Table 1) are heterogenous and limit use to strictly defined subgroups such as insomnia in adults over 55 years of age, or in children and adolescents with ADHD. These restrictions make it difficult for clinicians to treat a number of sleep disorders. Intrinsic circadian rhythm disorders such as DSWPD are present in young adults (indeed DSWPD most commonly starts in adolescence). There is therefore a need for a formulation with a license for younger adults. Similarly, there is a need for a formulation licensed for the treatment of circadian rhythm disorders such as jet lag. Single use of melatonin for short-term sedation under medical supervision to facilitate medical procedures such as electroencephalogram (EEG) is common across many hospital trusts in the UK, with significant resources used in each setting to explain and document the named patient provision of the product. Approval of this indication will allow melatonin use to be appropriately provided, recorded, and monitored through a national framework.

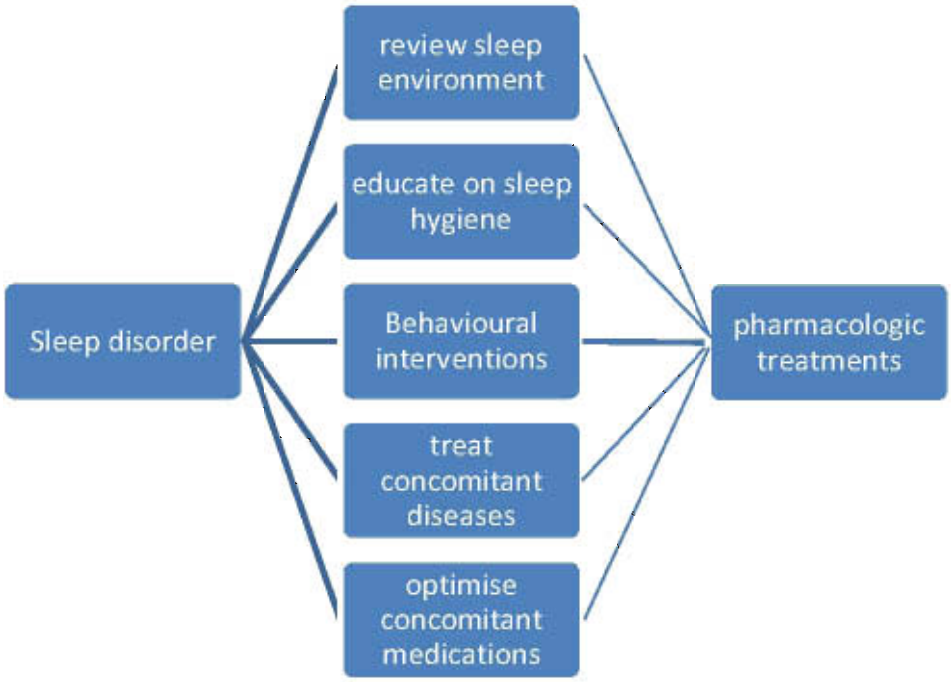


Figure 1 Interventions in sleep disorders

1.4 Regulatory Aspects

This Clinical Summary supports an Application for Marketing Authorization according to Regulation 54 (equivalent to Article 10a of Directive 2001/83/EC) considered as a bibliographic (well-established use) application.

In this bibliographic application, the Applicant presents the results of literature searches supporting the established pharmacokinetic (PK), pharmacodynamic (PD), efficacy and safety profile of melatonin in these indications and populations.

As required by a well-established use application, a bridge has also been built between the proposed product and those used in the studies in the literature on which the claims of safety and efficacy are based (described in detail in this clinical summary) and those in well-established use and this is described in detail in module 1.5.1 and the expert report provided within that module.

[redacted]

1.5 Clinical Product Development

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. It is secreted with a robust circadian rhythm, which in all species, whether nocturnal or diurnal, normally peaks during the dark phase of the

day. Melatonin, discovered in the late 1950s, has become a very popular substance over the past few decades. This compound has drawn attention in both the research setting, as a nutritional supplement and more recently as a medicinal product.

The sponsor has not conducted any new clinical studies.

This Clinical Overview is based on published scientific reviews and research articles, since melatonin has a long history of clinical use.

From searches of the [redacted] database using predefined search criteria, publications were reviewed to determine which were pertinent to this application. The literature search strategies are described in Table 2 and Appendix 2.7.2.5.1, Appendix 2.7.3.6.1, and Appendix 2.7.4.7, while individual summaries of all qualifying publications are provided in Module 2.7 (see Table 2).

[redacted]

2. OVERVIEW OF BIOPHARMACEUTICS

[redacted] ([redacted]). The plasma elimination half-life will be between 30 and 120 minutes and time to maximal concentration (T_{max}) for immediate release formulations is between 15 and 60 minutes.

[redacted]:

Intrinsic properties of melatonin drug substance – Solubility and Permeability

On all known data in the literature and published public assessment reports, melatonin is considered both highly soluble and highly permeable meaning that it meets the requirements of a BCS Class I compound in the guideline 'ICH M9 Guideline on Biopharmaceutics Classification system-based biowaivers' (EMA/CHMP/ICH/493213/ 2018; 10 February 2020).

[redacted]:

The studies and the data themselves are discussed in detail in the expert report from [redacted] (presented in module 1.5.1) but a bulleted summary of the results from the [redacted] (Report: [redacted] – Appendix I of Expert Report) and [redacted] (Report: [redacted] – Appendix II of Expert Report) is presented below:

Solubility:

- [redacted] melatonin drug substance can be considered highly soluble [redacted]
- [redacted]
- [redacted]

Permeability:

- [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
  - [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Based on all of the above the Applicant considers that a suitable bridge has been built between the proposed product and those used in the studies in the literature / approved and in well-established use and that further data / studies are unnecessary.

2.1 Biopharmaceutics Summary and Conclusions

Melatonin is a well-established active substance, with recognized efficacy and acceptable safety, and has been licensed in the EU for more than 10 years. No comparative bioavailability studies have been conducted by the Applicant and none are required for this application as the bridge to

the studies in the literature has been built, as above, [redacted]

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Melatonin is a well-established medicinal product with a known PK & PD profile as described in the summaries of product characteristics (SmPC) for the melatonin presentations currently licensed in the UK (Table 1). To confirm this profile, the applicant conducted systematic searches of the [redacted] database using predefined search and selection criteria (described in Section 2.7.2.1, Appendix 2.7.2.5.1 and Appendix 2.7.4.7), which identified 33 publications of relevance to PK and 28 relevant to PD. A systematic review by [redacted] included 22 studies (n = 359), and this was supplemented by 8 further publications on general PK. No publications were identified on immunogenic effects of melatonin indicating there is a low potential for hypersensitivity from the literature search results. Three additional publications ([redacted] described potential interactions. The PK publications included > 440 subjects, including 26 critically ill patients, 39 elderly and 64 paediatric patients. A short description of the basic pharmacokinetics and pharmacodynamics of melatonin is presented below followed by details of the literature.

Pharmacokinetics

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

Absorption

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

Distribution

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

Biotransformation

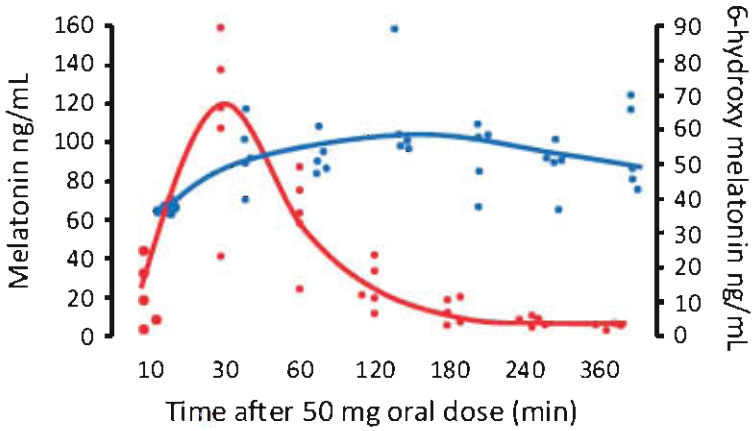
Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting ~ 80 – 90% of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting ~ 10% of melatonin metabolites recovered in the urine). 6-hydroxymelatonin undergoes sulphate conjugation (~70%) and glucuronide conjugation (~ 30%) prior to excretion. Melatonin metabolism is very rapid, with

plasma 6-hydroxymelatonin level rising within minutes of exogenous melatonin entering the systemic circulation.

The principal metabolite, 6-sulfatoxy-melatonin (6-SM), is inactive, and its urinary excretion reflects melatonin plasma concentrations ([redacted]). Plasma levels can be also measured directly or indirectly assessed through salivary measures. A reverse relation between bioavailability of melatonin and the 6-SM concentrations area under the curve has been shown, the low and variable bioavailability being explained by an important hepatic first pass metabolism ([redacted]).

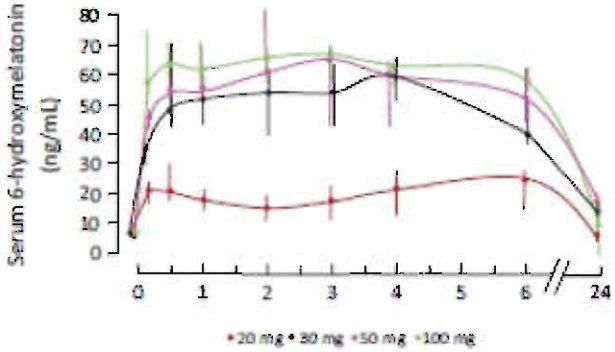
The pharmacokinetic properties of melatonin and 6-hydroxymelatonin have been studied in a phase 1, open-label, dose-escalation study in 20 healthy volunteers who were sequentially assigned to increasing doses of oral melatonin (20 to 100 mg) ([redacted] . Melatonin was detectable in serum as early as 10 minutes after taking oral melatonin and was rapidly cleared, with maximum levels reached at 30 to 60 minutes. The main metabolite 6-hydroxymelatonin sulfate was also detected in serum 10 minutes after drug administration with maximum levels reached at a median of 120 minutes and remained broadly stable between 1 and 6 hours but were back at baseline levels at 24 hours. Figure 2 illustrates the relationship between melatonin and 6-hydroxymelatonin in subjects who received a single oral dose of 50 mg of melatonin (N = 5). Figure 3 also shows the median and full range of serum 6-hydroxymelatonin levels over 6 hours after an oral dose of melatonin and shows a return to baseline at 24 hours. There was a significant effect of dose ($P = 0.028$) and levels after 30, 50 or 100 mg were significantly higher than after 20 mg (all $P < 0.001$).

Figure 2. Median Level of Melatonin (red) and 6-Hydroxymelatonin (blue) in Subjects Who Received a Single Dose of 50 mg Melatonin.



[redacted]

Figure 3 Median serum 6-hydroxymelatonin sulfate levels in healthy subjects over 6 hr after an oral dose of melatonin.



[redacted]

Metabolites of melatonin have antioxidant activity which increase the effect of melatonin administration as a free radical scavenger ([redacted] .

Elimination

Plasma elimination half-life (T½) is ~ 45 mins (normal range ~ 30 – 60 mins) in healthy adults. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than ~ 1% of a melatonin dose is excreted unchanged in urine.

Accumulation

The PK profile including the relatively short half-life and time to maximal concentration means the risk of accumulation is low particularly in someone with normal hepatic and renal function. This is also applicable for the major metabolites in the systemic circulation. As the PK is comparable in younger and older adults and half-life is generally not prolonged in the elderly this limits the potential for accumulation in the elderly.

One study in elderly patients ([redacted]), found that 1 a 3mg dose of immediate release melatonin could result in persistently high daytime concentrations the following day with the potential for accumulation. This is likely to reflect low metabolism or clearance of melatonin, as a result of either genetic polymorphisms, or reductions in hepatic or renal function. Melatonin accumulation is likely to result in high daytime levels of melatonin and present as persistent somnolence the following day despite sufficient sleep, or delay of the circadian rhythm.

Limited evidence exists that endogenous melatonin may accumulate in specific tissues for example epidermis [redacted]), mitochondria [redacted]) liver ([redacted] intestine and cerebral cortex [redacted] Additionally, these tissues may also be associated with accumulation of melatonin metabolites and involvement of local pathways for melatonin metabolism or degradation ([redacted]). Although the relevance of this to any potential exogenous melatonin accumulation in target tissues is not clear, no relevant clinical sequalae have been noted during the long history of melatonin use.

Linearity

Plasma melatonin Cmax and the plasma concentration-time curve (AUC) increase in a directly proportional, linear manner for oral doses of immediate-release melatonin in the range 3 – 6 mg whereas Tmax and plasma T½ remain constant. Dose linearity was demonstrated between 1 mg and 12 mg.

Inter- and Intra-subject Variability

Melatonin PK parameters exhibit significant variability both within and between subjects. Bioavailability estimates include: 1.7 – 4.7% ([redacted]), 15% ([redacted]), 15 to 20% ([redacted]), 10 to 56 % ([redacted]) and high variability has been reported by [redacted]) with greater inter-individual variability following 0.3 mg dose of melatonin among older volunteers (254.5 ± 145.7) than among the younger group (170.2 ± 22.0 pg/ml). [redacted] also showed dose that the ratio between serum and salivary melatonin varied up to 55-fold within and between individuals.

The high inter-individual variability is demonstrated by both the between group differences of ~ 17% in the mean values ([redacted] , but also by the size of the standard deviation (SD), particularly where one SD is greater than the mean value of the population ([redacted]).

Overall, the inter-individual variability has been estimated to be 50-70 % and the intra-variability at ~30-50%. The individual differences in circadian rhythm, absorption, distribution, metabolism and elimination between subjects contribute to the variability reported.

Effect of Food

Data on the effect of intake of food at or around the time of intake of melatonin are limited, but suggest that concomitant food intake may increase bioavailability almost 2-fold. [redacted]) found that melatonin plasma concentrations following a 2 mg gelatine capsule, solution or slow-release pill were higher in the fed than fasted state. However, the t_{max} values were similar and $T_{1/2}$ ranged from 32 (fasted stated) to 40 minutes (fed state). The difference in AUC in the fed state is unlikely to be clinically relevant due to the large inter-individual variations. No significant differences were found in the timing of peak plasma melatonin levels between these preparations in either the fasted or the fed state, t_{max} varied from 0.46± 0.07h (gelatine capsule fed), to 0.95±0.42h (solution, fasting, mean±s.e.mean)

Gender

Limited data described in Module 2.7.2 suggest that Cmax and AUC following ingestion of immediate-release melatonin may be higher (potentially roughly double) in women compared to men, however a large variability in the pharmacokinetics is observed. Plasma melatonin half-life does not appear to be significantly different in men and women.

Special populations

Children

Five studies in paediatric populations provide PK data and are described in Module 2.7.2. The studies by [redacted] (direct comparison between prepubertal and pubertal children and adults) and [redacted] (oral solution in children aged between 3-8) are most relevant.

[redacted] found a dose normalised (to 1 mg) C_{max} of 2505 pg/mL for 1 mg and 3855 pg/mL for 3 mg respectively using a liquid immediate-release formulation of melatonin. The corresponding AUC were 270780 pg.min/ml and 338560 pg.min/ml. This data does not suggest any meaningful difference between children and adults, and corresponds to the predicted PK variables of Ceyesto 1mg/ml based and on the PK data from the submitted adult studies.

[redacted] compared a 0.0005mg/kg intravenous dose of melatonin given to prepubertal and pubertal children, adult males and females (n=33; 6-31 years) to determine whether melatonin

pharmacokinetics change during puberty. The volume of distribution was similar for prepubertal and pubertal children (2.46L/kg and 2.31 L/kg), and possibly slightly higher than for the adult males (1.96L/kg) and adult females (1.89L/kg). Clearance in the adults was similar (males 0.030L/min/kg; females 0.029 L/min/kg) but appeared slightly higher in the children (prepubertal 0.044L/kg/min; pubertal 0.036 L/kg/min). This resulted in similar AUC for adult males and females (males 390.2 pg.min/ml; females 384.4 pg.min/ml), but slightly lower AUC in the children (prepubertal 250.9 pg.min/ml; pubertal 300.1 pg.min/ml).

The PK profile of oral melatonin in children compared to adults does not demonstrate any meaningful differences, and although, the PK profile can vary following intravenous administration, with a slightly lower exposure in children on comparison to adults, this is likely to be within the margin of variance and is unlikely to be of any clinical relevance.

Older people

Nighttime endogenous melatonin plasma concentration is lower in the elderly compared to young adults ([redacted]), particularly in patients with sleep problems [redacted]). Limited data for plasma-Tmax, Cmax, elimination half-life (T½), and AUC following ingestion of immediate-release melatonin do not indicate significant differences between younger adults and elderly persons in general ([redacted]), though the range of values (interindividual variability) for each parameter tend to be greater in the elderly. The pharmacokinetic variables Cmax, Tmax, T1/2, AUC, and Cl/F of melatonin were not significantly different between premenopausal and postmenopausal women ([redacted]).

However, it is not impossible that a decrease in CYP1A2 activity with age still results in higher plasma melatonin concentration for some patients [redacted] . In elderly patients with sleep disorders the group median (interquartile range) of peak endogenous melatonin concentrations was 25 (17–39) pg/ml [redacted] . Values stated for normal young subjects were with 100 pg/ml, and 35 pg/ml in older subjects [redacted]). Following administration of melatonin, there was a dose-dependent increase in circulating melatonin levels peaking approximately 1-2 hours after administration. Median (IQR) peak levels, observed on average within 2 h of treatment, were 84 (59–120) pg/ml, 220 (124–299) pg/ml, or 1370 (957–2440) pg/ml after administration of 0.1-, 0.3-, or 3.0mg IR doses, respectively. For the 0.1 mg and 0.3 mg doses melatonin levels returned to those seen after placebo by approximately 8-10 hours after administration, while sustained levels throughout the day were seen following the 3 mg dose. These sustained residual melatonin levels seen in some patients can benefit sleep during night-time, but can be counter-therapeutic if they persist during daytime.

Genetic polymorphisms

CYP1A2, CYP1A1 and CYP2C19, responsible for melatonin metabolism can be influenced by genetic and environmental factors. For CYP1A2, these can account for up to a 60-fold difference in activity which can affect both bioavailability and elimination. Tobacco by-products produced from smoking and oral contraceptive steroids have been well established as CYP1A2 inducers. Caffeine is also a common substrate of CYP1A2. Polymorphisms have been observed in the gene encoding CYP1A2, accounting for 16 known alleles. These genetic factors account for approximately 35% to 75% of the variation in CYP1A2 activity ([redacted] The frequency of these polymorphisms varies between different ethnic groups. A lower CYP1A2 activity has been found in Asian and African populations than in Caucasian populations. Among non-smokers, the frequency of polymorphisms was found to be 5% in Australian, 14% in Japanese, and 5% in Chinese people [redacted]). A number of loss-of-function alleles has been previously discovered for CYP2C19 and poor metabolisers typically carry two of these alleles. The frequency

of these genotypes ranged from 2 – 8 % of the tested populations and was highest in Asians [redacted]).

Three studies indicated altered pharmacokinetics are likely results from an altered metabolism by specific CYP-enzymes in the liver ([redacted]). Specific genotypes of cytochrome P450 (CYP) enzymes also altered pharmacokinetics ([redacted]) and can contribute to the possible variability across the population.

In general, the presence of polymorphisms across the different metabolic pathways encountered across different populations is unlikely to be of clinical relevance for melatonin. Melatonin is metabolised via multiple metabolic pathways and is not close to saturation. Melatonin itself has a wide safety margin, and there have been no known reports of significant pharmacogenomically related AEs or warnings.

Hepatic impairment

Although the route for metabolism and clearance of melatonin would suggest that hepatic impairment can reduce the clearance of exogenous melatonin, supporting clinical data are limited. In patients with cirrhosis and subclinical hepatic encephalopathy, an abnormal plasma melatonin pattern was seen compared with healthy controls. In the hepatically impaired, the onset of the increase in plasma melatonin levels and the melatonin peak during the night were both displaced to later hours. Furthermore, plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours ([redacted] . Serum T½ for exogenous melatonin in cirrhosis patients was double that of controls. Nocturnal urinary 6-sulphatoxymelatonin excretion in 21 hospitalized cirrhotic patients with normal renal function was significantly decreased compared with controls (median value of 8.28 µg, (range 0.85 to 28.1 µg) compared to 12.21 µg (range 9.12 to 29.04 µg; $P < 0.05$) ([redacted]). Due to the existing elevated melatonin levels, it is believed that patients with hepatic impairment, particularly those with more severe disease, are unlikely to benefit from therapy with oral melatonin.

Renal impairment

It is generally accepted that the main excretion route of the melatonin metabolites is renal. In rats and rabbits administered with labelled melatonin, 70 and 20% of the activity was excreted in the urine and faeces respectively after 24 hours [redacted] . Based on this, as melatonin metabolites are predominantly excreted in the urine, it can be expected that renal impairment may reduce elimination. However, supporting clinical data are limited with inadequate evidence to show that renal insufficiency does not impact melatonin elimination. A study on patients with end stage renal disease under chronic haemodialysis showed that melatonin plasma concentrations were comparable to those from healthy subjects ([redacted]). However, other stages of renal insufficiency not compensated with haemodialysis have not been studied. Therefore there is no clear evidence that renal insufficiency does not affect melatonin elimination.

Pharmacodynamics

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

Mechanism of action

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

Pharmacodynamic effects

The therapeutic properties of melatonin in the claimed indications are derived from a combination of its direct hypnotic effects and its chronobiotic effects. The time course of the direct hypnotic effects of melatonin are considered to closely follow the PK time profile. Peak hypnotic effects are seen from 30 to 90 minutes after administration of an immediate release formulation with sustained effects while significant amounts of melatonin remain in the systemic circulation. However, the window for effective hypnotic effect after administration of an immediate release formulation is relatively short (1-2 hours) ([redacted]).

The chronobiotic effects of melatonin have a far more complex time relationship, with antagonistic effects depending on when melatonin is administered within the existing melatonin circadian rhythm. For this element of melatonin's action, phase advance or delay of the endogenous dim light melatonin onset (DLMO) is a reliable and objective marker of clinical efficacy[redacted] . Within the overall rhythmic profile driven by the suprachiasmatic nucleus (SCN), the onset of melatonin secretion under dim light conditions (DLMO) is the single most accurate marker for assessing the circadian pacemaker, and is an established marker to evaluate problems related to the onset or offset of sleep and phase delays or advances of rhythms ([redacted]). DLMO is also a useful marker for identifying optimal application times for therapies such as exogenous melatonin treatment. The window for an effective advance of the circadian rhythm following administration of an immediate release formulation is larger (up to 7 hours before DLMO), with potentially greater effects to advance the DLMO with earlier administration [redacted] and extended effects on the circadian rhythm for days after administration ([redacted] see Module 2.7.3). Thus, in many indications, both the timing of administration and the dose strength is dependent on balancing the relative importance of the chronobiotic and hypnotic effects.

Other melatonin formulations approved for sleep disturbances, include prolonged release (PR) formulations, which have a different PK profile in comparison to immediate release formulations, often with an initial burst release followed by a sustained 'plateau' depending on the specific formulation. The initial absorption phase is similar but extended (supporting dosing 1-2h before bedtime) and the effects on sleep onset are considered driven by this initial increased level of melatonin. The sustained release property of PR formulations is usually intended to initiate and to maintain sleep throughout the night in individuals with insomnia. Immediate release melatonin is generally preferred for sleep induction ([redacted]) while prolonged release melatonin, which can have a continued effect for 8 to 9 hours, is preferred for sleep maintenance in the early morning. This prolonged effect can continue into the normal daytime part of the sleep cycle causing a 'hangover' effect in which the individual may feel drowsy or tired after waking up from a sleep cycle. This risk is reduced with immediate release formulations.

Careful management of the dose and formulation of melatonin are required in sleep disorders that include circadian misalignment. High levels of melatonin in the morning can prevent the phase advance, or may induce a phase delay[redacted] High residual levels of melatonin may occur in patients with lowered melatonin clearance such as the elderly, patients with renal or hepatic impairment, or genetic polmorphisms of the major metabolic pathways for melatonin metabolism. This is particularly likely at high doses and / or if a sustained release formulation has been administered. Immediate release formulations of melatonin are preferred in patients with circadian

misalignment such as DSWPD [redacted]). In cases where there is excessive morning sleepiness, a lack of effect on DLMO and / or advancing sleep phase the possibility of impaired melatonin clearance, too high a dose, or too late a time of administration should be considered.

The DLMO is not affected in all sleep disorders, but is an expected charateristic of any insomnia which includes a difficulty or delay in initiating sleep – the subtype of primary insomnia covered by the requested insomnia indications. In DSWPD the baseline DLMO is expected to be at least 2 hours delayed compared to environmental time, while in Jet Lag, the travel through the time zones has moved the local environmental time out of alignment with the pre-existing DLMO. DLMO is not an appropriate PD marker for studies in sedation.

Other PD measures include sleep assessments via objective measures such as polysomnography or actigraphy, and subjective measures such as sleep scores and sedation scores. The PD measures/markers which have been used to determine efficacy and relevance in the intended indications are both objective and subjective in nature. For sedation, PD measures include but are not limited to assessment of sedation scores, sleep onset latency, sleep duration, modified Yale Pre-operative Anxiety Scale (mYPAS) and steal induction. PD measures also included objective tests for cognition conducted during the recovery period such as colour cancellation test (CCT) and psychomotor performance tests such as finger tapping test (FTT). Changes in body temperature are also considered a PD variable.

The primary PD marker for the proposed indications is advancement in DLMO in the indications where there is circadian misalignment. This PD measure showed consistent results across the indications in populations with a significant phase shift or delay in sleep onset at baseline. Other PD measures to assess sleep onset such as assessment measures via PSG and actigraphy are also relevant measures, applicable to each indication and again showed consistent improvement both in model systems, and in the efficacy studies discussed below.

The hypnotic effect of melatonin to improve sleep onset was most effective when given in the evening and followed the time course of plasma melatonin levels. The chronobiotic effect of melatonin, assessed using 0.5 mg and 3.0 mg phase response curves showed that exogenous melatonin produces the largest advance shifts when circulating endogenous levels are low - at least 1-2 hrs before DLMO, with phase shifts diminishing when endogenous melatonin increases, and high levels in the early morning potentially delaying the circadian clock. Overall, no clear dose-relationship was found for melatonin.

3.1 Pharmacokinetic Literature

The PK literature is reviewed in detail in Section 2.7.2. The baseline characteristics of the pharmacokinetic publications reviewed are shown in Table 3. These include the 22 publications reviewed in the systematic review of [redacted] and 3 additional publications that meet the defined criteria. The pharmacokinetic variables for these publications are detailed in Table 4.

Table 3 Baseline Characteristics of PK Studies included in the Systematic Review.

Authors	No.	Study Design	Population	Measuring Period	PK Variables
[redacted]	12	Cohort study	HV	7 h	C_{max}, T_{max}, $T_{1/2}$, AUC
[redacted]	24	RCT	Critically ill	24 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl/F
[redacted]	33	Cohort study	HV	6 h	$T_{1/2}$, AUC, Cl/F, V_D
[redacted]	12	RCT	HV	8 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Bio
[redacted]	4	Cohort study	HV	-	$T_{1/2}$, Bio
[redacted]	12	Cohort study	HV	13 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl; Cl/F, V_D, V_D/F, Bio
[redacted]	27	RCT	Elderly	24 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl/F, V_D/F
[redacted]	12	RCT	HV	6 h	C_{max}, T_{max}, $T_{1/2}$, Cl/F
[redacted]	5	Cohort study	HV	28 h	C_{max}, $T_{1/2}$, AUC
[redacted]	29	Cohort study	HV	7 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl/F
[redacted]	15	RCT	HV	10.5 h	C_{max}, T_{max}, $T_{1/2}$, AUC
[redacted]	1	Case report	HV	-	T_{max}, $T_{1/2}$,
[redacted]	12	Cohort study	HV	24 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl/F, V_D/F
[redacted]	7	Cohort study	HV	2 h	C_{max}, $T_{1/2}$, AUC, Cl, V_D
[redacted]	18	Cohort study	HV	5 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl/F
[redacted]	12	Cohort Study	Critically ill	24 h	C_{max}, T_{max}, $T_{1/2}$, AUC,
[redacted]	60	Cohort study	HV	6 h	C_{max}, T_{max}, AUC,
[redacted]	7	Cohort study	HV	4 h	C_{max}, T_{max},
[redacted]	8	Cohort study	HV	6 h	C_{max}, T_{max}, AUC
[redacted]	5	Cohort study	HV	6 h	C_{max}, T_{max}, $T_{1/2}$,
[redacted]	8	Cohort study	HV	36 h	$T_{1/2}$, AUC
[redacted]	36	Cohort study	HV	9 h	C_{max}, T_{max}, AUC
[redacted]	12	Cohort study	HV	8 h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl, V_D, Bio
[redacted]	10	RCT	HV	12 h	C_{max}, T_{max},
[redacted]	12	Crossover Study	HV	10h	C_{max}, T_{max}, $T_{1/2}$, AUC, Cl/F

Baseline characteristics and reported pre-defined pharmacokinetic variables of the included studies. The symbol (–) refers to studies not reporting data.
RCT randomized clinical trial, h hours, C_{max} maximal plasma/serum concentration, T_{max} time to maximal plasma/serum concentration, $T_{1/2}$ elimination
half-life, Cl clearance, V_D volume of distribution, Cl/F clearance (oral), V_D/F volume of distribution (oral), Bio bioavailability.
Italicized authors are those from the 3 additional publications that meet the defined criteria from the systematic review.

Table 4 Pharmacokinetic variables of the included studies in the systematic review.

Authors	Melatonin dose /administration /route /subgroup	C_{max} pg/mL	T_{max} min	$T_{1/2}$ min	AUC pg/mL × min	Cl; Cl/F L/min	V_D; V_D/F L	Bio %
[redacted]	2 mg/oral/gelatin-coated capsules	Fasting, 2800	Fasting, 15	32	222,720	-	-	-
		Fed, 6800	Fed, 30	-	482,160	-	-	-
	2 mg/oral/slow-release pills	-	-	-	-	-	-	-
	2 mg/oral/corn-oil preparation	Fasting, 3500	Fasting, 30	-	237,180	-	-	-
		Fed, 4400	Fed, 30	40	349,560	-	-	-
[redacted]	10 mg/oral	14,974	30	88	1.80×10^6	5.85	-	-
[redacted]	0.0005 mg/kg BW/IV/prepubertal	-	-	40	15,054	3.30	185	-
	0.0005 mg/kg BW/IV/pubertal	-	-	47	18,006	2.70	173	-
	0.0005 mg/kg BW/IV/adults	-	-	47	22,614	2.03	135	-
[redacted]	2 mg/oral	2175	52	61	237.77×10^3	-	-	14
	4 mg/oral	5766	60	65	530.57×10^3	-	-	16
	2 mg/IV	96,850	-	60	1.63×10^6	-	-	-
[redacted]	0.5 mg/oral	-	-	47	-	-	-	33[a]
[redacted]	0.25 mg/oral/male	244	23	36	14,160	-	-	9
	0.25 mg/oral/female	624	23	45	42,084	-	-	17
	0.023 mg (250 mL/h)/IV infusion/male	124.8	113.4	36	15,288	1.57	73.1	-
	0.023 mg (250 mL/h)/IV infusion/female	169.0	110.4	41	21,846	1.09	53.8	-
[redacted]	0.4 mg/oral	405	78	108	95,700	6.32	1035	-
	4 mg/oral	3999	90	126	727.4×10^3	7.97	1602	-
[redacted]	6 mg/oral/+caffeine (smoker+non-smoker)	10,618	30	113	-	1.63	-	-
	6 mg/oral/−caffeine (smoker+non-smoker)	4480	60	106	-	3.08	-	-
[redacted]	5 mg/oral/+fluvoxamine	25,100	-	804[b]	8.48×10^6	-	-	-
	5 mg/oral/−fluvoxamine	2180	-	564[b]	372×10^3	-	-	-
[redacted]	6 mg/oral/wild-type[f] genotype+OC	7900	60	36	684×10^3	12.50	-	-
	6 mg/oral/wild-type genotype−OC	1800	60	37	138×10^3	132.50	-	-
	6 mg/oral/variant[f] genotype+OC[f]	7200	60	38	654×10^3	15.63	-	-
	6 mg/oral/variant genotype−OC	1700	45	49	144×10^3	94.00	-	-
[redacted]	5 mg/oral/immediate-release formulation (type A)	A = 4823	A = 30	A = 38	A = 256,885	-	-	-

Authors	Melatonin dose /administration /route /subgroup	C_{max} pg/mL	T_{max} min	$T_{1/2}$ min	AUC pg/mL × min	Cl; Cl/F L/min	V_D; V_D/F L	Bio %
	10 mg/oral/pulsatile-controlled release formulation (type B/C)	B = 3820 C = 4072	B = 45 C = 210	B = 48 C = 50	B = 507,911 C = 595,400	- -	- -	- -
[redacted]	Dose not reported/IV	-	4	44	-	-	-	-
[redacted]	5 mg/oral/slow-release	8770	167	91	2.3×10^6	3.09	451	-
[redacted]	0.005 mg/IV bolus 0.02 mg (10 mL/h)/IV infusion	- 72.1	- -	28 45	5400 -	0.97 0.97	35 63	- -
[redacted]	6 mg/oral/premenopausal women 6 mg/oral/postmenopausal women	16,756 16,438	30 53	46 52	1.18×10^6 1.24×10^6	8.44 9.88	- -	- -
[redacted]	3 mg/oral	11,040	16	94	1.69×10^6	-	-	-
[redacted]	1 mg/oral/powder 1 mg/oral/soft gel capsule 3 mg/oral/powder	799 2620 2405	60 60 40	- - -	2.10×10^7 5.53×10^7 62.5×10^5	- - -	- - -	- - -
[redacted]	3 mg/oral	3561	20	-	-	-	-	-
[redacted]	25 mg/oral/+smoking 25 mg/oral/−smoking	640 1858	90 90	-	102,419 294,002	- -	- -	- -
[redacted]	100 mg/oral	101,163	60	41	-	-	-	-
[redacted]	80 mg/oral 80 mg×3/oral	- -	- -	48 -	27.87×10^6 31.3×10^6	- -	- -	- -
[redacted]	0.3 mg/oral/age, 20–43 yrs 0.3 mg/oral/age, 49–73 yrs	170 255	48 45	- -	26,514 35,748	- -	- -	- -
[redacted]	10 mg/oral/gelatin capsule/male/ mean age, 27.1 yrs[e] 10 mg/IV/male/mean age, 27.1 yrs[e]	3550.5 389,875.0	40.8 -	53.7 39.4	281,538.3 14,179,767.6	- 0.0218	- 90[e] *[1.2 L/kg]*	2.5 -
[redacted]	5 mg/oral/immediate release formulation 5 mg/oral/controlled release formulation	23,352 4,690	< 60[d] -	- -	- -	- -	- -	- -
[redacted]	21 mg/oral/+ A.dahurica/male/age 27-36 yrs 21 mg/oral/- A.dahurica/male/age 27-36 yrs	169,000 *[169 ng/mL]* 39,600 *[39.6 ng/mL]*	77.4 *[1.29h]* 30.6 *[0.51h]*	94.8 *[1.58h]* 145.8 *[2.43h]*	12,983.3 *[779 ng/mL/h]* 1,016.7 *[61 ng/mL/h]*	1.1 *[66 L/h]* 14.6 *[875 L/h]*	- -	- -

The symbol (−) refers to studies not reporting the pre-defined pharmacokinetic variable, or not reporting a mean/median-data value of the specific variable. Dosages relate to the reported pharmacokinetic variables, not additional dosages administered in the same study. All values in square brackets, italicised refer to results from the original data, where conversion has been calculated for uniformity of units in Table Y.

C_{max} maximal plasma/serum concentration, T_{max} time to maximal plasma/serum concentration, $T_{1/2}$ elimination half-life, Cl clearance, V_D volume of distribution, Bio bioavailability, yrs years, BW body weight, IV intravenous, OC oral contraceptives

Italicized authors are those from the 3 additional publications that meet the defined criteria from the systematic review.

[a] Bioavailability was reported in the study. No other pharmacokinetic data for intravenous administration was reported.

[b] The reported values for $T_{1/2}$ must be due to an error, and is omitted from the manuscript.

[c] The investigated population age range of the patients has not been stated, however the age range for the inclusion criteria was 20-40 yrs.

[d] [redacted] does not report the exact T_{max} value, but reports the C_{max} was reached within the first hour of dosing.

[e] [redacted] reports the V_D in units of L/kg, which is presented in the table in square brackets. [redacted] has calculated any conversions for V_D to L based on a 75 kg adult and therefore 75kg has been used as the standard to convert this unit from 1.2 L/kg to 90 L for consistency.

[f] [redacted] recruited subjects screened for their CYP1A2 single nucleotide polymorphism. They were found homozygous for either the variant allele (-163A) referred to as the variant genotype or the wild-type allele (-163C) referred to as the wild-type genotype.

[g] AUC figures recalculated from the original paper. [redacted] reported AUC in units of µmol/L × min at 90516, 283200 and 26911 µmol/L × min for 1 mg powder, 1 mg capsule and 3 mg powder respectively. [redacted] had incorrectly calculated the conversion of these results to the standard units for the table of pg/mL × min at 2.11×10^{10}, 6.56×10^{10} and 62.5×10^{8} pg/mL × min in the respective formulations. However, the converted values are mis-calculated. An example of the correct calculation when applying the molecular weight of melatonin 232.28 g/mol is shown here for the 1 mg capsule. 238,200 µmol/L × min converts to 0.2382 mol/L × min. Multiply 0.2382 mol/L × min by the molecular weight 232.28 g/mol = 55.329 g/L × min. This is 55.329×10^{9} pg/L × min or 5.53×10^{7}.

Intrinsic Factors

Paediatric Population

Five publications in the paediatric population were identified by the PK literature search and discussed in Section 2.7.2.3.1, Table 5 and Table 6. There was one study with oral administration, one study with enteral administration and one study with intragastric administration. The PK parameters were consistent with those reported for healthy volunteers.

Elderly Population

Two of the publications identified by the PK literature search (Table 3, Table 4) were in elderly subjects. Both studies report PK parameters within the same range as those in healthy volunteers. [redacted] also suggested that there was no significant departure from linear kinetic behaviour in older subjects receiving oral melatonin across the studied dose range.

Other Intrinsic Factors

Two publications identified by the PK literature search (Table 3, Table 4) reported the impact of gender on the PK profile of melatonin. One ([redacted] reported higher bioavailability in females (17%), C_{max} (624 pg/mL) and AUC (42,084 pg/mL × min) compared to males (Bio, 9%; C_{max}, 244 pg/mL; AUC 14,160 pg/mL × min). This cohort study also reported an equivalent T_{max} (23 mins) between the genders, however the half-life ($T_{1/2}$) value was higher in females (45 mins) compared to males (36 mins). The other study [redacted]) reported no significant gender differences among the adults for any of the pharmacokinetic parameters on IV (intravenous) administration of very low doses of melatonin (0.0005 mg/kg BW).

One publication identified by the PK literature search (Table 3, Table 4) reported PK parameters in premenopausal (aged 20 to 33 years) and postmenopausal healthy women (aged 45 to 60 years) following 6 mg oral administration of melatonin ([redacted]). No significant differences between groups were identified for T_{max}, AUC, $T_{1/2}$, and clearance (oral) (Cl/F).

Table 5 Characteristics of studies in the systematic literature search in the paediatric population.

Authors	No. (Male, Female)	Study Design	Healthy Volunteer (HV)/patient characteristics	Measuring Period	PK Variables
[redacted]	5 (4M, 1F)	Cohort study	Neonates, with hypoxic- ischemic encephalopathy undergoing hypothermia	96 h	C_{max}, T_{max}, $T_{1/2}$, AUC, V_D, Cl/F
[redacted]	15 (8M, 7F)	Cohort study	Preterm Infants,	24 h	C_{max}, T_{max}, $T_{1/2}$, AUC
[redacted]	33 (Prepubertal: 5M, 4F Pubertal: 4M, 4F Adult: 9M, 7F)	Cohort study	HV	6 h	$T_{1/2}$, AUC, Cl/F, V_D
[redacted]	9 (7M, 2F)	Cohort study	Sleep onset insomnia in children (3-8 yrs) with autism spectrum disorders	8 h	C_{max}, T_{max}, $T_{1/2}$, AUC, V_D/F, Cl/F
[redacted]	18 (9M, 9F)	Cohort study	Preterm infants	Not stated	$T_{1/2}$, V_D, Cl

M, Male; F, Female; HV, Healthy volunteers; h hours, C_{max} maximal plasma/serum concentration, T_{max} time to maximal plasma/serum concentration, $T_{1/2}$ elimination half-life, Cl clearance, V_D volume of distribution, Cl/F clearance (oral), V_D/F volume of distribution (oral).

Table 6 Pharmacokinetic variables of the included studies in the systematic literature search in the paediatric population.

Authors	Melatonin dose /administration /route /subgroup	C_{max} pg/mL	T_{max} min	$T_{1/2}$ min	AUC pg/mL × min	Cl; Cl/F L/min[a]	V_D; V_D/F L[a]	Bio %
[redacted]	0.5 mg/kg /enteral infusion over 4 hours	0.27×10^6 *[0.27µg /mL]*	519.6 *[8.66 h]*	3,054 *[50.90 h]*	10.46×10^8 *[17.44 µg/mL/h]*	0.0035 *[0.21 L/h]*	*[5.67 L/kg]*	-
[redacted]	0.5 mg/kg / single intragastric	0.44×10^6 *[0.44 µg /mL]*	258 *[4.30h]*	656 *[10.94h]*	62.88×10^7 *[10.48 µg/mL/h]*			
	1 mg/kg / intragastric × 3 doses	1.03×10^6 *[1.03 µg /mL]*	174.6 *[2.91 h]*	562 *[9.37 h]*	13.36×10^8 *[22.26 µg/mL/h]*			
	5 mg/kg / intragastric x 3 doses	7.04×10^6 *[7.04 µg /mL]*	282 *[4.70 h]*	479 *[7.98 h]*	71.26×10^8 *[118.77 µg/mL/h]*			
[redacted]	0.0005 mg/kg BW/ IV/ prepubertal *[0.5 µg/kg]*	-	-	40 *[0.67 h]*	1.5054×10^4 *[250.9 pg/mL/h]*	*[0.044 L/min/kg]*	*[2.46 L/kg]*	-
	0.0005 mg/kg BW/IV/pubertal *[0.5 µg/kg]*	-	-	47 *[0.78 h]*	1.8006×10^4 *[300.1 pg/mL/h]*	*[0.036 L/min/kg]*	*[2.31 L/kg]*	-
	0.0005 mg/kg BW/IV/adult females *[0.5 µg/kg]*	-	-	48 *[0.81 h]*	2.3064×10^4 *[384.4 pg/mL/h]*	*[0.029 L/min/kg]*	*[1.89 L/kg]*	-
	0.0005 mg/kg BW/IV/adult males *[0.5 µg/kg]*	-	-	49 *[0.82 h]*	2.3412×10^4 *[390.2 pg/mL/h]*	*[0.030 L/min/kg]*	*[1.96 L/kg]*	-
[redacted]	1 mg /oral (n=8)	2,505	43.8 *[0.73 h]*	78 *[1.3 h]*	2.70780×10^5 *[4,513 pg/mL/h]*	*[14,205 mL/h/kg]*	*[28,778 mL/kg]*	-
	3 mg/oral (n=5)	11,566	33.6 *[0.56 h]*	58.2 *[0.97 h]*	1.015680×10^6 *[16,928 pg/mL/h]*	*[12,557 mL/h/kg]*	*[16,972 mL/kg]*	-
[redacted]	0.1 µg/kg/h / 2 and 6h infusion	-	-	1,014.6 *[16.91 h]*	-	*[0.045 L/h/0.867 kg]*	*[1.098 L/0.867 kg]*	-
	0.01 or 0.02 µg/kg/h / 2h infusion	-	-	1,261.2 *[21.02 h]*	-	*[0.012 L/h/0.867 kg]*	*[0.364 L/0.867 kg]*	-

The symbol (−) refers to studies not reporting the pre-defined pharmacokinetic variable, or not reporting a mean/median-data value of the specific variable. Dosages relate to the reported pharmacokinetic variables, not additional dosages administered in the same study.

All values in square brackets, italicised refer to results from the original data, where conversion has been calculated for uniformity of units in Table Y.

C_{max}, maximal plasma/serum concentration, T_{max} time to maximal plasma/serum concentration, $T_{1/2}$ elimination half-life, Cl clearance, V_D volume of distribution, bio bioavailability, yrs years, BW body weight, IV intravenous, h hours

[a] The parameters for V_D and Cl in children are expressed as per kg (bodyweight) due to the variability of weight across this group of subjects.

Effects of Extrinsic Factors

Three additional publications identified potential effects of extrinsic factors. The influence of caffeine and smoking status on the PK profile of oral 6 mg melatonin administration was assessed by [redacted] The study reported co-administration with caffeine resulting in increased C_{max} of 10,618 pg/mL, compared to 4480 pg/mL without caffeine. The T_{max} was reached quicker at 30 mins (with caffeine) compared to 60 mins (without caffeine), and the Cl was reduced to 1.63 L/min (with caffeine) compared to 3.08 L (without caffeine). The $T_{1/2}$ values remained unaffected by co-administration of caffeine. Caffeine was found to increase the oral bioavailability of melatonin and the publication suggested it was due to an inhibition of the CYP1A2 catalysed first-pass metabolism of melatonin. The study reports the effect was more pronounced in non-smokers. The influence of smoking on the PK profile of melatonin was reported by [redacted]. Following oral administration of 25 mg melatonin the study reported increased AUC values during the smoking free period (21.07 ± 7.28 nmol/L × h) compared to whilst smoking (7.34 ± 1.85 nmol/L × /h).

Studies reporting the interaction of other drugs with melatonin are described in Section 0

There is limited data suggesting that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. Therefore, Ceyesto 1 mg/ml Oral Solution should be taken at least 2 hs before and at least 2 hs after a meal; ideally at least 3 hs after meal by persons with significantly impaired glucose tolerance or diabetes (Refer to Overview of Safety Section 5.1).

Immunogenicity

No publications were identified on immunogenic effects of melatonin indicating there is a low potential for hypersensitivity with administration of melatonin from the literature search results.

3.2 Pharmacodynamic Literature

Systematic searches of the [redacted] database using predefined search and selection criteria (described in Section 2.7.2.1 and Appendix 2.7.4.7) identified 28 publications relevant to PD discussed below and summarised in Section 2.7.2.2.

Dosing-Effect-Relationship

Nine clinical studies reported no dose-effect relationship across a dosage range of 0.1 mg to 100 mg of oral melatonin in 328 subjects with regard to sleep, in both patients with sleep disorders and healthy volunteers [redacted]. A dose-effect-relationship with sleep was identified in [redacted] and [redacted]) in patients with treatment-resistant depression and healthy volunteers, respectively. The small sample size in both studies, and the single-blind randomised clinical trial (RCT) and open-label designs utilised by [redacted] and [redacted] respectively, may restrict the weight of these findings. One study [redacted] in patients with Parkinson's disease and sleep disturbances indicated that low (5 mg) and high doses (50 mg) of melatonin have a differential effect on subjective and objective measurements of sleep, respectively. [redacted] suggested that the modest effect in subjective sleep may be of clinical relevance in the population studied. Objective studies of sleep such as polysomnography (PSG) and subjective reports are often poorly correlated. This is particularly the case in insomnia, where the only relatively consistent objective finding is increased arousals. That means that objective

changes with medication may not be reflected in subjective benefits. As insomnia is very much a subjective disorder, the subjective experience is important in evaluating a therapy. Improvements in objective sleep are less relevant for the patient than the subjective benefits. This systematic review of the literature confirms that there is no clear dose-effect-relationship of melatonin at a population level with doses of 0.1-100 mg.

This systematic literature review indicates that the effectiveness of melatonin is developed at low doses, with a plateau effect as doses increase, whereby all doses exceeding a certain threshold dose are capable of inducing a similar level of response on sleep parameters.

The dose-effect-relationship of melatonin on the endogenous circadian rhythm was investigated in healthy volunteers ([redacted] and in free-running blind subjects [redacted]).

[redacted] determined using 0.5 mg and 3.0 mg to generate phase response curves and found that, if the doses were administered at the optimal time for each respective dose this elicits the same-sized phase shift regardless of the dose. One free-running totally blind subject, with the longest circadian rhythm out of the 7 subjects, unable to be entrained in the crossover study by [redacted] by a high daily dose (10 mg) was able to be entrained to 0.5 mg [redacted]. This, the authors theorised, was due to the excess melatonin in the 10mg condition spilling over into the wrong section of the phase-response curve [redacted]. Furthermore, [redacted] demonstrated using doses of 0.02-0.3 mg (20-300 µg) that 10 free-running totally blind subjects can be entrained to a normal circadian rhythm even at very low physiological doses. Additionally, [redacted] demonstrated in all 3 subjects (originally enrolled in [redacted] entrainment to the de novo dose of 0.5 mg. This contradicts the preliminary findings by [redacted] with no evidence to support the requirement of a higher dose of melatonin to initially capture free-running rhythms than is required for maintaining entrainment. [redacted] also established a significant log-linear relationship between the lowest entraining dose and the daily phase advance, indicating that a greater daily melatonin dose is required to entrain blind free-running subjects with longer circadian periods. [redacted] also demonstrated improvements in the time spent awake after the onset of sleep and sleep efficiency with melatonin after entrainment.

When used to facilitate sleep EEG recordings in 3 clinical studies across 636 children up to 18 years of age, melatonin was effective in ensuring that the sleep EEG could be completed (Melatonin 89.4% versus Triclofos 91.2%, [redacted]; Melatonin 73.3% versus Midazolam 36.7% [redacted] An augmentation dose of melatonin was needed in up to 25.4% of patients.
Age-related differences in the response to doses of melatonin were examined in 3 clinical studies. [redacted] reported a significant difference between age-stratified groups, with 2-6 year-old children with insomnia requiring 1.4 ± 0.6 mg, compared with 2.0 ± 0.7 mg among the 7-11-year-old group, and 2.8 + 1.4 mg in the 12-18-year-old group. However, [redacted] identified no association between age and melatonin dose response in children with autism and insomnia, and [redacted] found that age had no significant power to explain the drug effects in adults with developmental brain disorders and sleep disorders.

Cumulative Effect

In 3 studies encompassing children, adolescents and the elderly with insomnia a tendency for the effects of melatonin to be sufficient at 1-2 weeks was identified, with potentially further improvement with longer dosing. [redacted] identified on analysis of sleep latency with 1-3 mg melatonin a satisfactory response in the first week of intervention, with no significant difference in the second or third week. [redacted] noted in the majority

of patients with doses between 0.3-6 mg that although sleep onset improved with initiation, sleep patterns often did not normalize until 1-2 weeks into treatment and frequently required a dose adjustment [redacted] identified in the systematic review [redacted], demonstrated improvements in older adults in sleep maintenance with 2 mg sustained-release melatonin in 1 week, but with a further 2-month extension with 1 mg sustained-release melatonin further improvement was seen in sleep maintenance and sleep initiation also improved.

The timing required for successful entrainment of the circadian rhythm in free-running blind adult subjects was investigated in [redacted] and in the supplementary study by [redacted] These studies determined that for successful entrainment the optimal time to initiate treatment was when each subject's free-running rhythm was approaching a normal phase. Secondly, for entrainment to occur melatonin has to be given at a set time for a long enough period to encompass the entrainment point, that describes the moment when the circadian rhythm has drifted to the point where melatonin's advancing effect perfectly balances the natural tendency for the circadian rhythm to delay. Then, the endogenous pacemaker will lock on to the daily melatonin dose. The entrainment point will differ between subjects dependent on the phase the patient was in when the melatonin was started. Overall, the duration of treatment is dependent on the time taken to reach the treatment initiation point and the time required to meet the entrainment point, both of which are patient specific. This treatment strategy was successful in all subjects with appropriate doses for the length of their free-running circadian period.

Time-of-Day-Dependent Effect and Synchronisation with Circadian Rhythm

Overall, this literature review provides evidence of the importance of the time of administration of melatonin in relation to the endogenous circadian rhythm in order for effective treatment, and this is mirrored by the findings related to efficacy and safety. As described in 6 publications and Section 2.7.2.3.2 the timing of administration impacts the shift of sleep parameters and dim light melatonin onset (DLMO), and thus the effect of melatonin on sleep onset (SO), sleep onset latency (SOL), and DLMO. If exogenous melatonin is given when circulating endogenous levels are low this produces the largest advance shifts, with phase shifts diminishing when endogenous melatonin increases. Melatonin administration should be at least 1-2 hs before DLMO or the desired bedtime.

Carry-over Effects and Effects of Melatonin Discontinuation

From the PD literature search 9 publications [redacted] discuss melatonin discontinuation with regard to sleep. Additionally, the literature search identified four clinical studies that discuss these effects [redacted] in the context of the entrainment of the circadian rhythm and 2 publications [redacted].

The morning after administration, a possible carry over effect may occur, particularly with prolonged release melatonin, high doses, or in patients who are poor metabolisers. This prolongation of supra-physiological levels has been seen in older adults causing drowsiness, somnolence, or an unsteady feeling on awakening the following day [redacted] However, one meta-analysis [redacted] and 4 clinical studies [redacted] found no significant negative long-term residual effects of melatonin after administration with a dosage range of 0.1 mg-100 mg in both patients with sleep disorders and healthy volunteers. Similarly, in RSBD as stated by a consensus group of the French Medical and Research Sleep Society (SFRMS) in [redacted] in RSBD, immediate release

melatonin should be prescribed first as its side effect profile is much better than clonazepam shortly before bedtime. There is significant concern about the impact of benzodiazepines and other drugs on driving the morning after taking a dose. There is clear data showing that this is unsafe. There is therefore a need for hypnotics that don't impact on reaction times, attention or alertness the next day.

A short acting carry-over effect of melatonin when administered before placebo was investigated in 3 studies in patients with sleep disorders [redacted] identified in this systematic search, and in one study [redacted] in a separate search conducted to assess efficacy in RSBD. [redacted] and [redacted] with doses of 1-12 mg reported a carry-over effect of melatonin on sleep parameters, whereas [redacted] found no significant effect of treatment order with doses of 5 and 50 mg. [redacted] suggested this carry-over effect may result from the phase-shifting capacity of melatonin producing a beneficial effect by modulation of circadian rhythm, at least through the first days of the subsequent placebo phase.

Additionally, the literature review identified 3 clinical studies [redacted] that describe entrained blind free-running subjects reverting to the baseline pre-treatment period after the discontinuation of melatonin and suggests that subjects can rapidly be re-entrained with the appropriate dose and time of administration coinciding with the endogenous circadian phase. The supplementary paper by [redacted] expands on the discontinuation period in an open-label trial (with 0.5 mg after initial entrainment with 10 mg) with melatonin discontinuation in 2 subjects resulting in reversion to baseline free-running rhythms in 1 month and several days, respectively. This suggests the need for long-term treatment with melatonin to maintain entrainment to a normal 24-hour cycle, as blind free-running subjects revert to disordered circadian patterns on stopping melatonin.

Conclusions

This systematic review of the literature confirms that there is no clear dose-effect-relationship of oral melatonin at a population level with doses of 0.1-100 mg and that there is a tendency for the effects on sleep to be developed at low clinical doses (5-6 mg). The time of day that melatonin is administered is crucial for the resulting PD effects, with doses administered at their respective optimal times able to produce same-size phase shifts in the endogenous circadian pacemaker, with exogenous administration coinciding with high endogenous secretions resulting in diminished phase shifts and no further improvement in sleep parameters. For the effects of melatonin to be fully developed administration may need to take place over the course of several weeks. Overall, in order for oral melatonin to be effective the correct dosage, duration of treatment and appropriate time of day administration, with synchronization to the endogenous circadian rhythm, is required. Age-related differences may be present in the required dose of melatonin and the resulting dose response, but there is limited evidence for this. In the clinical studies identified in this systematic literature search no significant negative long-term carry-over effects of melatonin, with a dosage range of 0.1-100 mg, were identified in patients with sleep disorders or healthy volunteers. In order for circadian rhythm entrainment to a 24-hour cycle the dose needs to be tailored to the length of the individual's circadian period, that can be achieved with low physiological doses, with treatment initiation coinciding with the normal endogenous circadian phase and a treatment period long enough to encompass the entrainment point.

When used in single doses to facilitate EEG recordings, melatonin effectivenesss is increased when combined with sleep deprivation, and suitable surroundings to induce sleep. In clinical studies , an augmentation dose of melatonin was needed in up to 25.4% of patients.

3.3 Interactions

Thirteen publications from the systematic literature search, report interactions that involve melatonin, with four of these publications reporting the effect of the interaction on the pharmacokinetic profile of melatonin and 10 reporting a pharmacodynamic effect (Section 2.7.2). Two supplementary publications expand on melatonin drug interactions (Section 2.7.2).

A significant inhibitory effect of oral contraceptives on the CYP1A2-catalyzed melatonin metabolism was reported in one of these studies [redacted] Following 6 mg oral administration of melatonin, the study reported increased C_{max} (7200 to 7900 pg/mL) and AUC (654×10^3 to 684×10^3 pg/mL × min) for healthy volunteers taking oral contraceptives, compared to no oral contraceptive use (C_{max}, 1700 to 1800 pg/mL; AUC, 138×10^3 to 144×10^3 pg/mL × min), although this is unlikely to be significant in clinical practice.

An increase in the bioavailability of oral melatonin (dose, 5 mg) by coadministration of fluvoxamine has been reported in a cohort study of 5 healthy volunteers[redacted] The C_{max}, $T_{1/2}$, and AUC parameters are reported to have increased with the use of fluvoxamine.

The bioavailability of melatonin was increased by concomitant administration of *A. dahurica* extract and caused increased exposure and metabolic inhibition of melatonin following 21 mg of oral melatonin administration[redacted] *A. dahurica* is a coumarin found in herbal medicines, with strong inhibitory effects on melatonin metabolism.
Furthermore, two supplementary publications[redacted] expand on possible interactions between melatonin and concurrently administered drugs.
One study determined, by use of in vitro human hepatic post-mitochondrial preparations, that of the drugs screened only the potent CYP1A2 inhibitor 5-methoxypsoralen impaired melatonin metabolism at pharmacologically relevant concentrations and is likely to lead to clinical interactions; diazepam, tamoxifen and acetaminophen (paracetamol) did not impair the metabolic conversion of melatonin concentrations attained following therapeutic administration. Despite a marked, concentration-dependent, inhibition of melatonin metabolism observed with 17α-ethinyloestradiol, this is unlikely to result in an interaction following therapeutic intake of the steroid. Fluvoxamine was used as a positive control and demonstrated inhibition of melatonin metabolism at concentrations of 50 μM or higher, in a clinical setting this would indicate a possible impairment of melatonin metabolism that could lead to a rise in plasma levels[redacted].

In addition, one review publication stated that melatonin should be avoided in patients using warfarin, and possibly in patients taking other blood-thinning medications or with clotting disorders. The authors also warned that melatonin may cause drops in blood pressure, and that caution is advised in patients with high cholesterol levels, atherosclerosis, those at risk for cardiovascular disease, diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar[redacted]

Another study reported no pharmacokinetic interaction observed in subjects administered melatonin (2 mg oral prolonged release formulation) and zolpidem concomitantly. Melatonin alone had no effect on any cognitive measures, whereas zolpidem induced performance decrements on various cognitive tasks, which were even more pronounced when zolpidem was co-administered with melatonin. Regarding stimulated driving ability, the number of collisions was significantly increased with zolpidem and melatonin in combination with zolpidem, while melatonin alone did not have any significant effect[redacted]

An increase in sedation was reported in a case report following 3 mg oral melatonin administration, to a patient already taking citalopram, nortriptyline and oxycodone[redacted]

[redacted]. The patient improved on stopping melatonin and then sedation increased on re-challenge with melatonin.

Sleep quality ratings improved significantly during combined mirtazapine and 2 mg oral prolonged release melatonin intake and during subsequent intake of melatonin alone or together with very low doses of mirtazapine. The authors state that the application of mirtazapine followed by melatonin add-on and monotherapy improves sleep in perimenopausal women while evading mirtazapine-induced weight gain. It should be noted that although the authors suggest melatonin may play a role in preventing weight gain, this likely results from the tapering off of mirtazapine as opposed to the treatment with melatonin[redacted].

The Quality of Life in Childhood Epilepsy parental questionnaire demonstrated improvements in children with epilepsy administered add-on oral melatonin (6-9 mg, fast-release) to sodium valproate monotherapy on comparison of pre and post-treatment. Additionally, the median quality of life score post treatment in the sodium valproate and melatonin group presented a marginally significant difference in comparison to the sodium valproate and placebo group. The authors state that this suggests a potential use of melatonin as an adjunct to antiepileptic therapy to potentially improve quality of life in paediatric epilepsy[redacted]

Oral melatonin premedication, at a dose of either 3 or 5 mg, reduced the required dose of propofol for a sufficient level of hypnosis for tracheal intubation in patients undergoing surgery without prolongation of postoperative recovery room stay[redacted]

Oral melatonin (3-mg immediate-release) did not demonstrate efficacy on subjective assessment of wakefulness or sleep to reduce the use of anxiolytic benzodiazepines in elderly patients with minor sleep disturbance[redacted].

Furthermore, the systematic review by [redacted] identified 2 randomized, controlled, cross-over clinical studies in the elderly by [redacted] that assessed chronic insomniacs [redacted] and insomniacs all of which were chronic benzodiazepine users [redacted] Oral melatonin 2-mg (slow-release) was suggested, by the authors of the systematic review, to be more effective in the elderly insomniacs who chronically used benzodiazepines [redacted]

Concomitant administration of antidepressant medication (maintained at same dosage) and oral melatonin (5-10 mg, slow-release) resulted in a decrease in insomnia in 6 out of 8 patients with treatment-resistant depression [redacted] No additive effect of melatonin with fluoxetine were seen in manic depressive disorder [redacted]).

Alcohol can impair sleep, cause diuresis (which in turn may disturb sleep), potentially worsen certain symptoms of jet lag, insomnia and DSWPD e.g. headache, morning fatigue and concentration and have a sedative effect when consumed in large quantities, avoidance of alcohol is considered appropriate during melatonin treatment in these indications.

3.4 Clinical Pharmacology Summary and Conclusions

The literature reviewed is consistent with the known clinical pharmacology of melatonin and supports its use in the requested indications.

4. OVERVIEW OF EFFICACY

The clinical efficacy of melatonin in the treatment of sleep disorders has been established and proven by widespread usage over several decades. The demonstration of efficacy in the claimed indications is therefore based on reference to the clinical literature summarized in Section 2.7.3.

The sections below summarise the literature relating to DSWPD, insomnia in children and adolescents with ADHD, , for single use of melatonin for short-term sedation under medical

supervision to facilitate electroencephalograms in children and adolescents, and for use in jet lag in adults.

4.1 Delayed Sleep Wake Phase Disorder (DSWPD)

Definition of Pivotal Studies

[redacted]

Study Population and Design

The initial criteria related to the quality and size of the study and the criteria used to diagnose DSWPD. Delayed sleep phase syndrome (DSPS) or Delayed Sleep Wake Phase Disorder (DSWPD) are congruent entities defined by (i) International classification of diseases (ICD-11, 2019); (ii) Diagnostic and statistical manual of mental disorders (DSM-V, 2013) and (iii) International classification of sleep disorders (ICSD-3, 2014) as a disorder in which a person's sleep is delayed by two hours or more beyond what is considered an acceptable or conventional bedtime. The diagnostic criteria for these disorders were very disparate prior to a harmonisation process initiated in 2010. Although minor differences in terminology remain (DSP-Type in DSM-V and DSWPD in ICSD-3 and ICD-11), the diagnostic criteria are now harmonised between the classification systems, which were previously very different. The delayed sleep then causes difficulty in being able to wake up at the desired time, but other aspects of sleep, such as arousals, quality of sleep, total sleep time (TST) and sleep architecture may not be significantly changed [redacted] which is why these parameters are not generally required in the diagnostic process. The underlying sleep disturbance is a misalignment of the circadian rhythm. In treating this, melatonin has both a chronobiotic and a hypnotic effect [redacted]

DSWPD has a strong overlap with chronic sleep onset insomnia (SOI) and the disease states may be indistinguishable, particularly where DLMO is not determined. Both sleep disorders are characterised by complaints of inability to fall asleep at the desired clock time, accompanied with problems in daytime functioning [redacted] Consequently, DSWPD may be underdiagnosed. In the pivotal studies by [redacted], the populations of children which the authors described as having symptoms characteristic of DSWPD were described as 'CSOI with late melatonin onset', partly due to the changes in the diagnostic criteria underway at the time. This subset of children with chronic SOI show a delay in markers of the circadian pacemaker, such as DLMO, which is indicative of DSWPD, and therefore despite this can also be described as chronic SOI with late melatonin onset (AASM ISCD-3 (2015), [redacted]). Both studies, have also been recently reviewed by the French Medical and Research Sleep Society (SFRMS) and considered to provide Grade A evidence in support of the use of melatonin in DSWPD [redacted]. They are also included in a recent review [redacted] thus independently validating the suitability of these studies to inform treatment decisions in DSWPD. [redacted]

[redacted]

Definition of Minimum Clinically Important Difference (MCID) in sleep studies

The definition of a minimum clinically important difference (MCID) can be approached in a number of ways, each of which has inherent advantages [redacted]

The primary intent of treatment of DSWPD with the proposed product is to correct the misalignment of the circadian rhythm. The chronobiotic effect of melatonin is effective when given as much as 7 hours before the misaligned endogenous increase, without persistent high levels of melatonin into the morning hours. The clinical correlate for the main objective of treatment is the sleep onset time in patients who choose their own bedtime (frequently older adolescents / young adults) or the sleep onset latency in those with a fixed bedtime (frequently children). Careful management of the dose and formulation of melatonin are required as high levels of melatonin in the morning can prevent the phase advance or may induce a phase delay [redacted] The secondary effect of the proposed product in DSWPD is support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect). TST, quality of sleep, arousal time and sleep architecture are very much considered secondary in DSWPD, but are evaluated in some studies. These effects are similar across all sleep disorders and populations and closely follow the plasma levels of melatonin.

For SOL and SOT, various values have been set previously with the HTA assessment by [redacted] and various systematic reviews [redacted] setting an MCID of 30 minutes for SOL in general sleep disorders. [redacted] considered that SOT improvement of 27 minutes, SOL of 24 minutes and DLMO of 44 minutes were clinically relevant in children with CSOI, including those with late DLMO, as they improved mean values to within the normal ranges found previously in children with ADHD without insomnia [redacted] or healthy children [redacted]. Specifically within circadian rhythm disorders, the American Academy of Sleep Medicine (AASM) Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders [redacted] set MCID of 15 minutes for SOL and SOT with 30 minutes for the shift in circadian rhythm (DLMO). [redacted]

Pivotal Studies in DSWPD

Using these criteria, 5 publications reporting 4 studies, with a combined population of 312 patients aged from 6 to 65 years, were considered pivotal in DSWPD (Table 9, Table 10). These studies, [redacted] are considered positive pivotal studies on which the proposed indication and posology can be based. A further 6 publications were not considered pivotal as they were of cross-over design. These studies, which also supported the efficacy and safety of melatonin for the treatment of DSWPD, are not summarised in this clinical overview.

Discussion of Pivotal Studies

Primary Efficacy Endpoint of SOL / SOT

The pivotal studies demonstrated a clinically and statistically significant improvement in the alignment of the patients' sleep schedules in relation to environmental time (Table 7) through

SOT (if sleeping when tired) or SOL (if having chosen a fixed desired bedtime). This was seen across the range of doses and age groups in the pivotal studies where doses and timing of melatonin administration varied between studies and was often individualised or based on the desired bedtime (DBT). In each of the studies, the diagnosis was based on the ICSD-2 definitions or equivalent and was validated at baseline through a mixture of physician interviews, sleep diaries, or sleep assessments in the clinic. A minimum duration of symptoms was required in all studies, with a delay in sleep onset, or phase shift of dim-light melatonin onset (DLMO) relative to DBT. Improvements in other sleep parameters were also reported, but in DSWPD these disturbances are secondary to the circadian misalignment and so are secondary endpoints.

Table 7 Effect of Melatonin on Sleep Onset Times (SOT) or Sleep Onset Latency (SOL) in Pivotal Studies in Delayed Sleep Wake Phase Disorder

Study	Dose of Melatonin	Melatonin	Placebo	Difference	P value
[redacted]	3mg (n=10)	-74 min	-49 min	-25 min	<0.01
[redacted]	0.5mg (n=10)	-122 min	-83 min	-44 min	<0.001
[redacted]	0.05 mg/kg (n=16)	NR	NR	-42 min	<0.001
	0.1 mg/kg (n=19)	NR		-50 min	<0.001
	0.15 mg/kg (n=18)	NR		-56 min	<0.001
[redacted]	3mg (n=30)	-39 minute	+5 min	-44 min	<0.01

[redacted] investigated the effect of 0.5 mg fast-release melatonin given 1h before DBT on a variable number of nights per week over 28 days in newly recruited DSWPD patients. The results focus on the 104 subjects (66.3%) taking capsules for at least 5 consecutive nights per week on at least 3 of the 4 weeks (only 5.0% took capsules for 7 nights per week on all weeks).

[redacted] applied a gradually advancing rise time to all of the newly recruited DSWPD patients, with a 4-arm comparison of placebo, morning bright light, 3mg IR melatonin 12h after waking (not before 8pm), or combination treatment with melatonin and bright light.

[redacted] reported a randomized, placebo-controlled double-blind, parallel group trial where children with chronic sleep onset insomnia (n=72) and late melatonin onset (validating the diagnosis of DSPS) received either IR melatonin 0.05, 0.1, and 0.15 mg/kg or placebo, at least 1-2h before DLMO and before DBT, during 1 week. The authors have confirmed that the participants would meet the current criteria for DSWPD.

[redacted] reported a randomized, placebo-controlled double-blind, parallel group trial where children with chronic sleep onset insomnia (n=84) and late melatonin onset (indicative of DSWPD – confirmed by the author) received 3mg IR melatonin (at 19:00h), placebo, or light therapy for 3-4 weeks.

Significant earlier **sleep onset times** were reported in the melatonin treatment groups when compared to placebo ([redacted], p=0.013; [redacted] p<0.001; [redacted] a >30 min improvement; [redacted] a 44 minute improvement . p<0.01).

[redacted] reported that sleep diary data showed that the treatment group had earlier bed (p=0.013) and rise times (p < 0.0005) as well as less Total Wake Time (TWT) (p=0.003). With respect to actigraphy, TWT was significantly reduced compared to baseline assessment in the treatment group (p=0.005).

[redacted] found significantly shorter SOT with melatonin. The SOT based on the diary data reduced by 83 minutes with placebo (95% CI: −99 to −66 min, p <0.001) and by 122 min with melatonin (95% CI: −139 to −106 min, p <0.001) with a treatment difference of 44 minutes in favour of melatonin (95% CI: −66 to −21 min, p <0.001). SOT was also significantly shorter based on actigraphic data with an improvement of 34 minutes for melatonin compared with placebo (95% CI −60 to −8 min, p = 0.011). SOL was also statistically significantly improved with melatonin compared to placebo for both the diary (-18.2-min, 95% CI −30.78 to −5.59, p = 0.005) and actigraphic measurements (-11.9 min, 95% CI −19.54 to −4.39, p = 0.002). The beneficial effects of melatonin were confirmed by post hoc sensitivity analyses.

[redacted] found a significant difference to placebo at all doses for both sleep onset and sleep onset latency. The sample size calculation was based on sleep onset. This improved by 42 to 56 minutes across the 3 dose groups. The 0.05 mg/kg group improved by 0:42 ±0:10 min (95% CI 0:20 to 1:03, p <0.001) compared to placebo, the 0.10 mg/kg group by 0:50 ±0:11 min (95% CI 0:27 to 1:13, p <0.001 and the 0.15 mg/kg group by 0:56 ±0:10 (95% CI 0:34 to 1:18, p <0.001).

[redacted] found that melatonin treatment decreased sleep latency (sleep diary; p < 0.01) and advanced sleep onset (sleep diary and actigraphy; p<0.01).

As can be observed, for all four pivotal studies, SOT / SOL was improved in the groups treated with immediate release melatonin by the clinically relevant time [redacted]

The distribution of response across the population is provided in Figure 4, reproduced from [redacted] (a red line has been added to indicate the more stringent responder criteria of 1h for DLMO and 30 minutes for SOT and SOL). When considering the 0.10 and 0.15 mg/kg dose groups, >75% of subjects had a response greater than this for SOT and SOL with the upper quartile of the population having responses above 1h for SOT and SOL. As previously recognised for insomnia in ADHD [redacted] the individual patient response is an important consideration.

Figure 4 Distribution of response in [redacted]

In studies that assessed onset of effect, beneficial effects were evident within 1 week in most patients, with almost all patients experiencing benefit by 4 weeks. Relapse / recurrence after

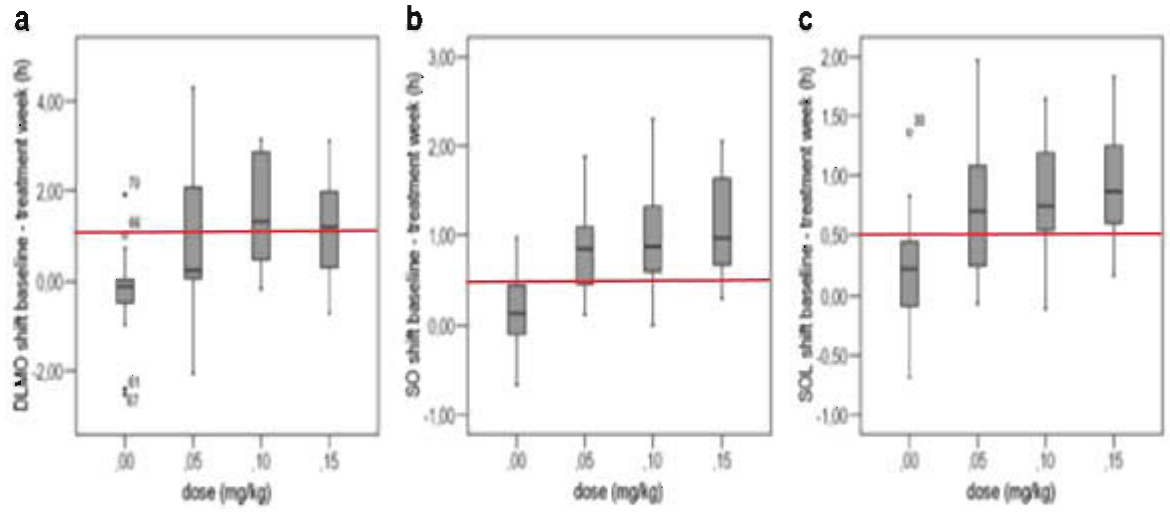


Fig. **a** DLMO (threshold=4 pg/ml) advance (individual differences between baseline and treatment week) in the four treatment groups. **b** SO shift (individual differences between baseline and treatment week) in the four treatment groups. **c** SOL reduction (individual differences baseline and treatment week) in the four treatment groups. *Solid box* upper and lower quartiles, *box length* contains the middle 50% of the data (IQR); *line* median, *lines extending from box (whiskers)* the distance to the largest and smallest observations that are less than one quartile range from the box, *dots O* outliers (>1.5×IQR)× =extremes (>3×IQR). *DLMO* dim light melatonin onset, *SO* sleep onset, *SOL* sleep onset latency

cessation of treatment was common. However,in one study [redacted] more than 25% were able to maintain their phase advance for 2 months to over 1 year while off treatment.

In studies that assessed onset of effect, beneficial effects were evident within 1 week in most patients, with almost all patients experiencing benefit by 4 weeks. Relapse / recurrence after cessation of treatment was common. However,in one study [redacted] more than 25% were able to maintain their phase advance for 2 months to over 1 year while off treatment.

DLMO

[redacted] found that DLMO advanced by 0.73 ± 1.21 h following melatonin, compared to 0.24 ± 1.11 h following placebo (P > 0.05). [redacted] found a phase advance of DLMO in all groups with an overall estimated mean (SD) of 23:56h (74) at baseline compared to 21:56h (117) at the two-week assessment and no significant interaction by treatment. Van [redacted] found that treatment with melatonin significantly advanced DLMO by 1:05h at 0.05 mg/kg (P=0.053), 1:45h at 0.10 mg/kg (P<0.001) and 1:31h at 0.15 mg/kg (P<0.001). [redacted] found that DLMO improved from 21:15 (1:02) to 19:44 (1:26) in the melatonin groups compared to the placebo group where the change was from 21:00 (1:24) to 20:51 (1:14) (P=0.01).

Although DLMO advance is not considered a primary clinical efficacy parameter, DLMO is considered the gold standard for assessing changes in circadian rhythm and is a reliable and objective marker of clinical efficacy [redacted]. The fact that melatonin has a significant effect in DLMO advance, which is consistent with the MCID for this parameter, is considered further strong supporting evidence that the proposed treatment is effective in DSWPD.

Alertness, Fatigue & Cognition

Immediate release melatonin had beneficial effects on some measures of alertness, fatigue or cognition in the pivotal studies. These are likely secondary effects of normalising sleep onset and hence total sleep time. There were no hang-over effects or negative impact on cognition in any study of immediate release melatonin in DSWPD. [redacted] showed that melatonin treatment resulted in significantly lower PROMIS score for sleep-related impairment at week

1 (P = 0.035), week 3 (P = 0.042), and week 4 (P = 0.018). [redacted] showed a reduction in subjective sleepiness and fatigue and an improvement in working memory/processing speed variables and executive function measures in all groups.

Efficacy Conclusion

The four pivotal studies demonstrate the efficacy of immediate release melatonin in the treatment of DSWPD in children and adolescents and into young adulthood in both the primary end-point of SOL / SOT but also in multiple secondary end-points including TST.

Age Range

It is proposed that the indication will be limited to children and adolescents aged 6-17 and young adults up to the age of 25. The proposed age ranges align with the prevalence of delayed sleep-wake phase disorder (DSWPD) which is seen to be highest in adolescents and young adults, with rates estimated between 3.3 and 4.6 percent compared to lower prevalence in older adults with estimates between 0.2 to 1.7 percent [redacted] The natural history of DSWPD is such that it typically emerges in late childhood or during adolescence, and without treatment it may be a chronic condition that persists into adulthood. (AASM ISCD- 3 2014). Age-related circadian rhythm changes, including phase advancement, may lessen the propensity for delayed sleep phase in later adulthood explaining why the prevalence declines and the lessened need for melatonin to be initiated in in older adult populations [redacted]

Efficacy in Children Aged 6-12 Years

Two pivotal studies ([redacted] demonstrated efficacy in DSWPD in this age group with [redacted] including patients between 6-12 years old (mean: 8.95) and [redacted] those between 7-12 (mean: 9.92). As such efficacy in this age group is considered assured.

Efficacy in Adolescents Aged 13-17 Years

[redacted] which demonstrate efficacy in DSWPD included patients of between 16-25 (mean: 20.75) and 17-64 (median: 26) years respectively. These studies thus demonstrate efficacy in patients aged between 16-17. Although none of the proposed pivotal studies specifically cover the small age range of 13-15, it is not unreasonable to consider that this population can be bridged by the two pivotal studies either side of this age range – [redacted] on the lower side and [redacted] on the upper side. Indeed, [redacted] described in Module 2.7.3, is a placebo-controlled cross-over study of 1 mg immediate release melatonin in 21 subjects of 14–19 years showing an advance time of sleep onset by 68 min. This study was considered to provide Grade A evidence by the SFRMS recommendations [redacted]

Young adults (18-25 years)

The demonstration of efficacy in [redacted] included patients between 16-25 years (mean: 20.75) which fully supports the age range for young adults of 18-25. This is further supported by [redacted] which had a much larger age range of 17-64 but had a median of 26 years indicating that the majority of the population were younger adults (Median IQR ranged from 21-31 and 24-36 depending on treatment group).

In summary, a proposed age range of between 6-25 years is considered both fully representative of the populations studied in the pivotal studies and to include the majority of patients diagnosed with DSWPD.

Posology

Following update of the indication and review of the pivotal studies the Applicant is proposing the following posology for DSWPD:

In children and adolescents (6-17 years) and adults up to 25 years of age:

The recommended starting dose is 1 to 2 mg once every day, 1-2 hours before the fixed desired bedtime, given as 1-2 ml of Ceyesto 1 mg/ml Oral Solution. The dose of melatonin can be increased by 1mg until effective up to a maximum of 5mg (5ml) per day, independent of age. The lowest effective dose should be sought.

After 6 weeks of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. In patients with significant continuing daytime sleepiness or misaligned circadian rhythm the possibility of high residual melatonin in the morning should be considered. In these cases melatonin can be stopped and restarted at a lower dose. The dose that adequately alleviates symptoms should be taken for the shortest period. There is insufficient safety data to support long term use of melatonin in children approaching puberty. After the achievement of advanced sleep-wake phase for 6 weeks, treatment should be stopped to evaluate if the patient can independently maintain an advanced sleep-wake schedule. If withdrawal of melatonin results in clinical relapse, melatonin can be resumed and continued.

Limited data are available for up to 3 years of treatment (please see section 4.4).

Adults over 25 years of age

In adults whose symptoms persist past the age of 25 and who have shown clear benefit from treatment, it may be appropriate to continue treatment. However, initiation of treatment with Ceyesto in adults over 25 years of age is not appropriate (see sections 4.4 and 5.1).

The dose and time of dose used in the four pivotal studies are outlined in Table 8.

Table 8 Dose and Time of Dose in Pivotal Studies in DSWPD

Study	Dose of Melatonin	Timing of Dose
[redacted]	3mg (n=10)	12 hours after waking up but not before 8pm
[redacted]	0.5mg (n=10)	1 hour before DBT
[redacted]	0.05 mg/kg (n=16)	1-2 hours before DBT
	0.1 mg/kg (n=19)	
	0.15 mg/kg (n=18)	
[redacted]	3mg (n=30)	At 7pm

Justification of appropriate dose range

The proposed starting dose of 1-2mg to be given 1-2 hours before the desired bedtime with 1mg increases up to a maximum of 5mg are based on that used by [redacted] at a dose of 0.1mg/kg as there did not appear to be a significant difference / benefit with the higher dose of 0.15mg/kg in this study. The dose range for the patients on 0.1mg/kg was calculated from the patients' weight as from 1.4 to 4.9mg with a mean dose of 2.91mg. This is similar to the

effective dose used by [redacted] and [redacted] of 3mg per day. It is noted that [redacted] used and demonstrated efficacy at a dose of 0.5mg however this study included older patients outside of the proposed age range.

Justification of appropriate timing of dose

The proposed timing of the dose i.e. 1-2 hours before the desired bedtime is fully supported by both [redacted] and is considered aligned with (or at least not contradictory to) [redacted] / [redacted].

Continuation of treatment in adults beyond 25 years of age

A statement has been included that treatment can be continued for patients aged over 25 years of age whose symptoms persist and who demonstrate a clear benefit from treatment. This is based on the continuing efficacy in the older patients described by [redacted] supportive studies described in Module 2.7.3, and current clinical practice where consensus guidance recommends the use of melatonin in adults with an established diagnosis and who require treatment [redacted] and in the recommendations from the [redacted] and the [redacted]

Whilst prevalence of DSWPD is highest in adolescents and young adults, with rates estimated between 3.3 and 4.6 percent [redacted]),

DSWPD is also present in older adults, with estimates between 0.2 to 1.7 percent [redacted]. The natural history of DSWPD is such that it typically emerges in late childhood or during adolescence, and without treatment it may be a chronic condition that persists into adulthood (AASM ISCD- 3 2014). Age-related circadian rhythm changes, including phase advancement, may lessen the propensity for delayed sleep phase in later adulthood explaining why the prevalence declines and the lessened need for melatonin to be initiated in in older adult populations [redacted]).

It is evident from this review that immediate release melatonin as would be provided by the Applicant's proposed product is an effective treatment for DSWPD in children, adolescents and young adults who have had an inadequate response to sleep hygiene measures, achieving improvements in sleep onset time or latency, which correspond to the proof of concept illustrated by the phase advance of DLMO, and by the beneficial effects on multiple domains of patient well-being, which are likely secondary effects of normalising sleep onset and hence total sleep time. Four pivotal studies demonstrate efficacy in the proposed population.

Safety

Adverse events reported in the pivotal studies in DSWPD, and the other studies described in Module 2.7, were consistent with the known safety profile of melatonin and did not raise any new safety concerns. Additional tabulations of the safety data from these studies have been included in Module 2.7.4.

[redacted] reported that side effects were captured at 2 weeks and 3 months. Of the 5 patients who withdrew during the study, one reported the reason as 'Adverse events during treatment period, exhausted, did not want to continue participation in the study' but the treatment group for this subject was not specified. Side effects at 2 weeks were reported by 15 participants: 6 in the combination group, 2 in the melatonin group, 4 in the bright light group, and 3 in the placebo group (p = 0.409). Side effects reported were headache (n = 5), nausea (n = 3), discomfort in the eyes (n = 5), and

skin irritation (n = 2). Side effects at 3 months were reported by 3 participants: headache (n = 1) and discomfort in the eyes (n = 2). The authors did not attribute the side effects to specific treatment groups. None of the side effects were serious or long lasting.

[redacted] reported that most AEs occurred at similar rates between treatment groups (Light-headedness Mel=2, Pla=2; Daytime sleepiness Mel=2, Pla=1; Decreased libido Mel=2, Headache Mel=1; Vivid dreams and/or nightmares Mel=1, Pla=4). No deaths or SAE were reported for either treatment group, and no participants discontinued due to AE.

[redacted] did not provide specific information on safety variables, but did not report the occurrence of any AE. The study noted that wake-after-sleep-onset (WASO) increased in some children during melatonin treatment but noted that this could be due to the high 3mg starting dose as increased WASO can often be resolved by lowering the melatonin dose .

[redacted] reported that the most common adverse events were red cheeks, red earlobes, and red eyes and yawning within an hour after administration (n=15); pale looks, dizziness, and cold feelings (eight); headache (two); nausea and stomachache (one); and dizziness and nausea (one). Most of the adverse events wore off during the treatment week. Headache and stomach ache were reported in the placebo group, not in the melatonin-treatment groups. The sleep-related adverse events (red cheeks or rather pale looks, cold feelings) and dizziness were reported in the three melatonin groups; the frequency was related to dosage (0.15:0.1:0.05=5:4:3). One participant ended the treatment period early due to bedwetting, attributed to the medication by his mother (0.05 mg/kg). Two other participants reported enhanced urination during the evening and night (0.1 and 0.15 mg/kg).

Safety Conclusion

Melatonin is a well-established active substance licensed in the EU for more than 15 years, with a recognized acceptable safety profile in children, adults and the elderly. The overall bibliographic application includes data from more than 10,000 patients treated with melatonin (Module 2.7.4), and all studies referenced in the application were reviewed for safety. Melatonin has been studied in a broad range of patients and at a wide range of doses with very few adverse events recorded. Side effects resolve on cessation of the medication and there is no clear evidence of any long term side effects. Adverse events reported in the DSWPD studies were consistent with the known safety profile of melatonin and did not raise any new safety concerns. The most frequently reported AEs were headache and nausea. Immediate release melatonin had minimal or positive impacts on daytime performance and alertness when taken as described in the SmPC.

Overview of Well-Established Use

Immediate release melatonin has been used for at least 10 years within the EU / UK for the treatment of DSWPD. This is illustrated in Figure 5 - a graphic in the form of a timeline of the use of melatonin in the treatment of DSWPD in Europe / UK. Immediate release melatonin has been used for the treatment of DSWPD since the early 2000s with NHS trust documents dating from as early as 2003-2004 [redacted] but that interest, research and importantly use has continued with pivotal studies published in 2010, 2014, 2017 and 2018 and multiple NHS guidance documents on the use of melatonin in DSWPD between 2004 and the present day, with examples shown in Table 11. It should be taken noted that in the absence of a licensed product, the guidance documents would be written considering strengths / dosage forms available. As such the proposal to e.g. start at 3mg and increase to 6mg (then 9mg and 12mg) is likely to be related to the available strengths / forms rather than a specific desire to use those particular doses:

The well-established use of melatonin is also reviewed by [redacted] This review concluded that melatonin is an efficacious and safe chronobiotic drug for the treatment of DSPD in children, provided that it is administered at the correct time (3-5 h before endogenous melatonin starts to rise in dim light (DLMO)), and in the correct (minimal effective) dose. As the status of circadian rhythmicity may change during long-time treatment, it was recommended to stop melatonin treatment at least once a year (preferably during the summer holidays).

Additional consensus guidance based on the recommendations of the French Medical and Research Sleep Society (SFRMS) has been reported [redacted] Members of the MEL consensus group of the SFRMS comprised 11 expert sleep physicians / researchers who analysed the scientific literature available on [redacted] for use of melatonin in circadian sleep/wake rhythm disorders. Studies were classified according to their level of proof [redacted] from Grade A to C and the experts gave a ruling on formalised recommendations to help practitioners in their consideration of prescriptions. The populations included were based on the ICSD 3rd edition criteria - a significant delay in the phase of the major sleep episode in relation to sleep and waking desired or necessary times, with symptoms lasting for at least 3 months, considering that when patients can choose their schedules freely, they exhibit good quality and duration of sleep. While adolescents were considered particularly susceptible the expert panel recognised that the disorder was also present in adults with 40% of cases having possible autosomal dominant inheritance including polymorphisms of the PER3 clock gene [redacted]

The expert panel made a Grade A recommendation for the use of melatonin in DSWPD in children and adults. They considered that there were 6 Grade A studies in children and 3 in adults, with a further 2 studies mentioned contributing to the recommendations. All studies used immediate release melatonin and the experts considered that globally the best impact of immediate release melatonin concerned sleep-onset latency, sleep-onset time and advance in DLMO. Considering the balance between chronobiotic and soporific effect, the maximum chronobiotic effect is time dependent (6 and 4 hours before usual bedtime) while the soporific effect is obtained half an hour before desired sleep onset. Concerning duration of treatment, a minimum of four to six weeks of treatment was considered necessary to reset the biological clock to the new schedules. The committee suggests re-evaluating the patient and in case of recurrence treatment may be prolonged with a therapeutic washout of at least one week between treatments. Treatment should be reassessed once a year. The experts considered that there were no standard dosages and recommended dosage be increased from 0.5 to 5 mg, excluding higher dosages because of the risk of 'spillover effect'. At treatment initiation immediate release melatonin 0.5 mg (chronobiotic) should be given 4 to 6 hours before usual sleep time (chronobiotic), if necessary, a soporific dosage of 1 to 5 mg added half an hour before desired bedtime (small chronobiotic effect and more soporific effect).

A further recent systematic review and meta-analysis [redacted] was developed by experts (including the UK, Netherlands, US and Canada. The analysis included stratification by age, indication and other parameters. In consideration of the evidence in DSWPD in children, adolescents and adults, the mean difference in effect in DSWPD presented by [redacted] was seen to be significant for both SOL Diary and SOL Actigraphy with a similar effect size on SOL Actigraphy (which is significant) in children and adolescents with DSWPD, as there is in children and adolescents with insomnia in ADHD.

DSWPD Conclusion

The 4 pivotal studies included 308 subjects with an age range of 6-65 years. Clinically and statistically significant improvements in SOT or SOL were reported in the melatonin treatment groups when compared to placebo [redacted] 25 minute improvement p=0.013; [redacted], 44 minute improvement p<0.001; [redacted] a >30 min improvement, p<0.001; [redacted] a 44 minute improvement . p<0.01). Similar effects were seen for dim light melatonin onset (DLMO) a marker of circadian rhythmicity.

The critical appraisal of the literature and updated benefit risk analysis demonstrates the efficacy and safety of immediate release melatonin for treatment DSWPD in children, adolescents and young adults. Melatonin has been in well-established medicinal use for DSWPD within the EU for more than 10 years, with recognized efficacy and an acceptable level of safety. Based on the analysis of the peer-reviewed literature on the current knowledge on efficacy and safety of melatonin in DSWPD, the benefit/risk ratio of melatonin is considered to be positive.

Table 9 Design of Pivotal Studies of Melatonin in Delayed Sleep Wake Phase Disorder

Stndy	N [n] /Age	Melatonin Dose/ Formnlation/ Dnration	Design	Popnlation	Endpoints
PIVOTAL					
[redacted]	40 [38] 16-25y	3mg IR (Kragerø /Asmnan Inc) 12 h after awakening, bnt not before 8 pm, or placebo x2w + Olx3m	R-PC-DB-PG 4aim bright light / dim light +OLFU No WO Period	Newly recrnited patients ICSD DSPD	Actigraphy, sleep diaries, SOL, WASO, EMA, TWT, TST and SE, PSQI, Bergen insomnia scale, DLMO. Snbjective sleepiness and fatigne (KSS, ESS, and FQ), objective sleepiness/aronsal (AAT), cognitive tests (CPT-II, WAIS-III subtests, and D-KEFS subtests), side-effects
[redacted]	116 16-65y	0.5mg IR (Pnre Encapsnlations) 1h before desired bedtime x4w	R-PC-DB-PG	Newly recruited patients and sleep clinic patients; ICSD DSPD confirmed at baseline with DLMO after, or <30 min before DBT	Primary: actigraphic SOT; Actigraphy: SE, subjective sleep-related daytime impairment, sleep distnrbance, measures of daytime sleepiness, change in illness severity, DLMO, AE
[redacted]	72 6-12y	0.05, 0.1, and 0.15 mg/kg IR (Pharma Nord), at least 1-2h before DLMO and before DBT x 1 week	R-PC-DB-PG	Medically referred patients with DSPS or insomnia+ADHD, with delayed DLMO, not responsive to sleep hygiene	The stndy was powered to detect a advance (SD) in sleep onset of 67 (85) min compared to an advance (SD) of 10 (46) min in the placebo gronp Sleep was assessed with log and actigraphy. Outcomes were the shifts in DLMO, SO, and SOL.
[redacted]	84 7-12y	3mg IR (Pharma Nord) (N=26) at 19:00 h., placebo, (N=28), or light therapy (N=30) (3-4 weeks)	R-PC-DB-PG	Children with chronic sleep onset insomnia and late DLMO	Actigraphy, sleep diaries, SOL, SOT, TST, SE, WASO, DLMO

AAT= Alpha Attennation Test, AE= Adverse Events, CES-D= Centre for Epidemiologic Stndies Depression, CGI= Clinical Global Impression, CPT= Cognitive Processing Therapy, CR= Controlled Release, DBT= Desired Bedtime, D-KEFS= Delis-Kaplan Execntive Fnnction System, DLMO= Dim Light Melatonin Onset, DSPD = Delayed Sleep Phase Disorder, DSPS= Delayed Sleep Phase Syndrome, ESS= Epworth Sleepiness Scale, FQ= Fatigne Qnestionnaire, ICSD= International Classification of Sleep Disorders, ISM= Impaired Sleep Maintenance , IR=Immediate-release, KSS= Karolinska Sleepiness Scale, NDD= Nenro-developmental Disabilities, NR= Not Reported, REM= Rapid Eye Movement, SD= Standard Deviation, SE=Sleep Efficiency, SO= Sleep Onset, SOL= Sleep Onset Latency, SOT= Sleep Onset Time, SR= Snstained Release, TST= Total Sleep Time, TWK= Total Wake Time, WAIS= Wechsler Adnlt Intelligence Scale, WASO= Wakefulness after Sleep Onset, WT= Wake Time.

Table 10 Efficacy of Melatonin in Pivotal Studies in Delayed Sleep Wake Phase Disorder - Selected Endpoints

Stndy	N [n]/ Sex /Age	Arm or Epoch	Alertness/fatigne/ cognition	Change from baseline					
				Sleep onset time (SOT) (h) or Sleep onset latency (SOL) (m)	Wake time (WT) or wake after sleep onset (WASO)	Total sleep time	Temperatnre	DLMO	UaMT6s
PIVOTAL									
	116 16-65y	Baseline Melatonin Gronp[c]	Improved sleep related impairment	01:32 ± 1:54	WASO: 45.44 ± 26.38	6.62 ± 1.65	ND	22:46 ± 1:12	ND
		Baseline Placebo Group		01:20 ± 01:49	49.81 ± 25.84	6.80 ± 1.51	ND	22:52 ± 1:27	ND
		0.5mg IR 1h before desired bedtime x4w		00:03 ± 1:37	50.31 ± 30.13	7.24 ± 1.39	ND	-	ND
		Placebo		00:17 ± 1:44	57.82 ± 29.96	7.17 ± 1.45	ND	-	ND
	40 [38] 16-25 years	Placebo (n=10)	Improved sleepiness and fatigne	SOL Baseline: 19±15 2 Week: 24±11	Baseline: 60±15 2 Week:43±16	Baseline:448±53 2 Week:391±58	ND	-	ND
		Bright Light (n=10)		Baseline:19±11 2 Week: 15±10	Baseline:59±27 2 Week:47±22	Baseline:429±47 2 Week:375±64	ND	-	ND
		3mg IR x2w + Olx3m Bright (n=10)		Baseline: 23±19 2 Week: 21±19 3 Month:	Baseline:50±20 2 Week:45±19	Baseline:433±62 2 Week:405±49	ND	-	ND
		Combination (n=10)		Baseline: 23±13 2 Week:11±8	Baseline:52±23 2 Week:41±16	Baseline:448±66 2 Week:393±45	ND	-	ND
	70 30M: 42F 6-11.8 years	Placebo (n=17)	ND	-	Baseline: 7:38 ± 0:16 2 week: 7:48 ± 0:24	ND	ND		ND
		0.05 mg/kg (n=16)		0:31[a] ± 0:10**	Baseline: 7:41 ± 0:32 2 week: 7:39 ± 0:25			1:05[b] ± 0:32	
		0.1 mg/kg (n=19)		0:31 ± 0:10**	Baseline: 7:41 ± 0:25 2 week: 7:41 ± 0:26			1:45 ± 0:26	
		0.15 mg/kg (n=18)		0:42 ± 0:09***	Baseline: 7:41 ± 0:18 2 week: 7:32 ± 0:26			1:31 ± 0:24	
	84 51M: 33F 7-12y	Placebo (n=28)	ND	ΔSOT +5 min	-4.36 min	-0.09h	ND	+0.05h	ND
		3mg Melatonin (n=30)		ΔSOT -39 minnte**	+7.15 min	+0.39h**		-0.99h**	
		Light Therapy (n=26)		ΔSOT -13 min	-2.8 min	+0.01h		+0.03h	

CR= Controlled Release, DLMO= Dim Light Melatonin Onset, DSPS= Delayed Sleep Phase Syndrome, IR= Immediate Release, NR = Not Reported, ND = Not Done, OL= Open Label, OLFU= Open-label follow-np, SOL = Sleep Onset Latency, SOT= Sleep Onset Time, SR= Snstained Release.

* = P<0.05, **=P<0.01, all for melatonin versus placebo. #=P<0.05, ##=P<0.01, ###=P<0.001, all vs baseline

[a] SOL shift, Mean difference in comparison to placebo gronp reported.

[b] DLMO shift, Mean difference in comparison to placebo gronp reported

[C] Difference between treatment gronps' change from baseline to treatment

[redacted]

Table 11. NHS Documents Supporting Well-established Use of Melatonin in DSWPD

Organisation	Form of melatonin	Dose	Indication	Guidance	Document type	Year
[redacted]	Immediate Release Tablets	3mg-9mg	Delayed Sleep onset	**Initial trial: 7 to 14 days:** 3mg tablets daily Give 30 minutes before bedtime, preferably on an empty stomach. It can take up to an hour to be effective. If non response (delayed time to sleep onset, disturbed sleep, early morning awakening), increase to 6mg or 9mg (maximum dose). Extra benefits of doses above 9mg are uncertain.	Formulary Guidleines	2020
[redacted]	Prolonged Release Tablets Immediate Release Tablets / Oral Solution	2mg-10mg	Delayed sleep phase syndrome in children	Initiate at 2mg 1-2 hours before bedtime. Swallow tablet whole with plenty of water. Increase dosage according to response. Dose can be increased to 4-6mg daily after 1-2 weeks. Maximum BNFC dose 10mg Treatment should be discontinued every 6 months to assess if it is still beneficial.	Shared Care Guidance	2019
[redacted]	Immediate Release Capsules	3mg 10mg	Sleep disturbances in children to help establish normal sleeping pattern	Melatonin capsules should be given 30 – 60 minutes before bedtime as directed by doctor	Patient Leaflet	2006
[redacted]	Immediate Release Tablets Prolonged Release Tablets	3mg IR 2mg PR	Treatment of Sleep-Wake Cycle Disorders	There is significant clinical experience with the use of melatonin for the treatment of paediatric sleep-wake cycle disorders. Results in terms of improved sleep patterns have been generally favourable and adverse effects minimal. Recommended starting dose – BioMelatonin®: 3mg (IR tablets) given 20-30 minutes before desired sleep time, Circadin®: 2mg 1-2 hours before desired sleep time. Immediate release preparation should be trialled initially. If there has been an insufficient response after 7-10 days, consider increasing dose to 6mg. In some cases a dose of 9mg may be tried although additional benefit of doses above 6mg is uncertain. If child is unable to swallow tablets, Bio-Melatonin® will dissolve in a small amount of water if broken and stirred. For children who continue to have a fragmented sleep pattern after an initial two-week trial, consider using sustained release preparation. The licensed prolonged-release tablet Circadin® is the only preparation for children requiring a sustained relief product; this cannot be crushed as this destroys the matrix, however can be cut in half and swallowed without chewing.	Shared Care Protocol	2009
[redacted]	Tablets / Capsules	2-3mg; increase to 4-6mg. Maximum of 9-12mg	Melatonin for delayed sleep phase disorder	Melatonin has been prescribed for children and young people who have problems with sleeping, when other methods have not worked The usual starting dose is 2-3mg for all ages, this may be increased to 4-6mg if limited or no improvement is found after one to two weeks. Rarely 9-12mg has been tried but if no benefit is seen after two weeks on the higher dose then the	Patient Information	2010

		in rare cases		melatonin should be stopped. If it is found to be useful it should be continued for several months.		
[redacted]	Immediate Release Oral Solution Prolonged Release Tablets (can be crushed)	2mg-10mg	For the treatment of sleep-wake cycle disorders in children and young adults. With the aims of improving the onset and duration of sleep and establishing a regular nocturnal sleep pattern	For children aged from 1 to 18 years an initial dose of 2 – 3mg is recommended. Immediate release preparations (oral solution or crushed modified release tablets) should be taken 30 – 60 minutes before bedtime and modified release tablets should be given after food, 1 – 2 hours before bedtime. In the absence of improvement after 1 – 2 weeks the dose can be increased to 4 – 6 mg at night. The maximum dose is generally accepted to be 10mg but higher doses have been used. Treatment should be stopped in those that fail to demonstrate a response to the maximum dose.	Shared Care Guideline	2015
[redacted]	All forms	2-10mg	Melatonin for delayed sleep phase disorder	Initially 2-3mg increased if necessary after 1-2 weeks to 4-6mg at night. Maximum dose 10mg at night.	Public health evidence-based summary	2011
[redacted]	1mg/ml Oral Solution	2-10mg	Delayed Sleep Phase Syndrome	Initially 2-3 mg daily for 1-2 weeks then increased if necessary to 4-6 mg before bed time. Maximum 10 mg per day. To be given 30-60 minutes before bedtime.	Shared Care Guideline	2021
[redacted]	Modified release tablets 1mg/ml Oral Soluton	6-10mg	Sleep disorders in paediatrics (children and adolescents)	A total daily dose of melatonin up to 6mg daily is usually sufficient. Maximum of 10mg	Shared Care Guideline	2020

4.2 Insomnia in Attention Deficit Hyperactivity Disorder (ADHD)

Critical Appraisal of Pivotal Studies

[redacted] Using these criteria, 3 studies were considered pivotal in children with ADHD alone and 5 studies were considered supportive in children with ADHD alone. A further 24 studies were considered supportive in children with ADHD mixed with other NDDs.

Of the 3 pivotal studies, all were randomized, placebo-controlled and double blind, with 1 of three being a crossover design and 2 of three studies continuing with an open-label treatment. In the cross-over study, the treatment length was for 10 days including a wash out period of 5 days. The authors justified the small wash out period by melatonin's short PK half-life. However, a carry-over of treatment effect from an initial melatonin phase to a second placebo phase is possible and would reduce any observed treatment effect. As this would be bias towards no effect, and underestimate the treatment effect, it is not considered a significant concern for any studies that demonstrate efficacy.

The dose of immediate release melatonin used in the pivotal studies were either 5 or 6 mg and the open-label follow-up periods were 3 months – 5 years. The timing of melatonin administration varied between studies from either 20-minutes before bedtime or at a fixed time at 7pm.

On review of the pivotal studies it is evident that, the efficacy of immediate release melatonin to improve sleep has been demonstrated in children and adolescents with chronic insomnia and ADHD. Benefits have been demonstrated on sleep onset time, sleep onset latency, advances in DLMO and increased total sleep time. Based on the totality of evidence from these pivotal studies the Applicant has proposed that Ceyesto treatment should only be initiated in patients who have had an inadequate response to sleep hygiene measures, reflecting both non-responders and patients who relapsed following use of sleep hygiene.

The dose that adequately alleviates symptoms should be taken for the shortest period. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen.

All 5 supportive studies observed improvements in alertness, fatigue or cognition with melatonin at varying doses. In those studies assessing sleep, improvements in total sleep time and sleep onset latency were also improved. Finally, an improvement in DLMO, a PD marker, was also observed by [redacted] compared to baseline with the melatonin (3 or 6 mg) group.

In short the supportive studies all endorse the Applicant's proposed indication and posology.

The Applicant designated other studies in mixed populations including both patients with ADHD and those with other comorbidities such as autism, learning disabilities, intellectual disability (also known as mental retardation), conduct disorders, cerebral palsy, and impairments in vision and hearing as supportive studies.

Discussion of Benefit Risk for insomnia in children and adolescents with ADHD

Table 12 provides key study design elements including, reported indication, melatonin formulation, dose regimen including timing of melatonin administration and treatment duration, study population, sample size, and primary endpoint. Table 13 summarises the efficacy of melatonin on selected endpoints across the studies in children with ADHD. The general efficacy findings for melatonin across the studies in children with ADHD is described in Module 2.7.3. For the assessment of efficacy, pivotal studies were defined as randomised, controlled studies with an appropriate sample size based on the use of objective or subjective endpoints, or study design elements such as a cross-over design in contrast to a parallel group design. Pivotal studies were also limited to those with a homogeneous population diagnosed with ADHD.

Insomnia in Children with ADHD

Pivotal Studies in ADHD

Study Designs

Three studies were designated as pivotal based on a homogeneous population with ADHD. All were randomised, double blinded and placebo controlled studies. The largest study [redacted] included 105 children with ADHD with chronic sleep onset insomnia aged between 6 and 12 years old. The children were given 3 or 6 mg melatonin or placebo over 4 weeks. [redacted] included children with ADHD already treated with Ritalin and aged from 7 to 12 years (n = 50) and who were given 3 or 6 mg melatonin and Ritalin (1mg/kg) ± placebo over an eight week period. The third pivotal study [redacted] included ADHD patients aged from 6 to 14 years old who were given 5 mg melatonin or placebo for a 30 day cross over period. The time of administration varied between studies, with [redacted] giving melatonin at 7pm before a free bedtime, while [redacted] administered melatonin 20 minutes before a fixed desired bedtime in association with sleep hygiene measures.

All three pivotal studies included sleep as primary endpoints. In [redacted], children's appetite and sleep were evaluated in weeks 0, 2, 4 and 8 using ADHD rating scale, Sleep Disturbance Score for Children (SDSC), and appetite questionnaires. In comparison, [redacted] assessed sleep using actigraphy and sleep logs. The actigraphy data was converted into sleep parameters including sleep onset, sleep latency, wake up time, total time asleep, sleep efficiency and moving time. In addition, [redacted] included an assessment of dim light melatonin onset (DLMO) at baseline and on the first evening of the fourth treatment week using saliva samples. [redacted] evaluated the efficacy of sleep hygiene and melatonin treatment for insomnia in children with ADHD. Twenty- seven children were evaluated in this 2-phase treatment study that started with a sleep hygiene intervention. Only children who continued to have initial insomnia of >60 minutes were then eligible to enter the double-blind, randomized, placebo-controlled, crossover trial. Melatonin 5 mg was administered 20 minutes before bedtime.

Sleep Onset Time or Latency

An improvement in the initiation of children's sleep was observed in all three pivotal studies with a shortened sleep onset time observed.

In the large parallel-group pivotal study [redacted] melatonin was seen to advance sleep onset time by 26.9 ±47.8 minutes) whereas in the placebo group sleep onset was delayed by 10.5 ±37.4 minutes ($p < .0001$), [redacted] giving a clinically

significant difference between the groups. The responder rate (advance of sleep onset >30 minutes in children with actigraphy data) was also higher for melatonin: 20/41 (48.8%) compared to 5/39 (12.8%) after placebo (x2 = 12.0; p = .001). The melatonin group also showed a significant decrease in sleep latency compared to placebo (-21.3 ± 33.0 compared to +3.0 ± 31.7; p=.001).

In the cross-over pivotal study [redacted] melatonin was clinically (16 minutes) and statistically significantly superior to placebo on actigraph measurement of sleep-onset latency (SOL), t (18) =-4.54, p < .01). Mean somnolog SOL on placebo was 62.1 minutes (SD = 26.6) versus mean SOL on melatonin of 46.4 minutes (SD = 26.4). There was no carry-over effect between periods. This indicates that a significant effect on SOL is obtained within the first 10 days of treatment, and that the direct effects of melatonin on sleep have stopped after 5 days without treatment. Of the 19 patients who completed the randomized part of the study, 17 showed benefit from melatonin and continued into open-label follow-up. The authors state that children responded to melatonin in a manner that was clinically and statistically significant versus placebo, based on actigraph measurement of sleep-onset latency (mean: 16 minutes, p < .01). There was only 1 severe adverse event of a migraine. Overall, melatonin was statistically and clinically superior to placebo in reducing insomnia.

In [redacted] (Table 13), sleep onset time was observed as 23.15 ±15.25 minutes before treatment and 17.96 ±11.66 after treatment (p = 0.047) .

Total Sleep Time

Total sleep time was also assessed as part of sleep endpoints with total sleep increasing in all 3 pivotal studies. [redacted] reported that total time asleep increased with melatonin (19.8 ± 61.9 minutes) versus placebo (13.6 ± 50.6 minutes; p = .01). A significant change compared to baseline was also observed in [redacted] with p = 0.06. [redacted] demonstrated a treatment difference between the melatonin and placebo periods on a somnolog measure of total night-time sleep, where more time asleep (15.0 minutes) was evident during melatonin treatment (p < .01) while the actigraph measurements of total sleep did not reach a significant treatment between the 2 week treatment periods.

DLMO and other PD markers

DLMO was assessed in one pivotal study (Table 13). [redacted], assessed DLMO at baseline and on the first evening of the fourth treatment week using saliva samples taken hourly from 6:00 to 10:00 PM (6 to 7 years old), or 7:00 to 11:00 PM (8 to 12 years old) in dim light. DLMO was defined as the linearly interpolated time at which the melatonin concentration first reached 4 pg/mL. Mean baseline DLMO was approximately 1 hour before sleep onset in both groups. In this study, melatonin-treated children showed an advance in DLMO of 44.4 ± 67.9 minutes compared with a delay of 12.8 ± 60.0 minutes in children receiving placebo. The treatment difference was clinically and statistically significant (p < 0.0001), and the authors commented that melatonin shifted DLMO in these children to normal values (found previously in children with ADHD without insomnia). In melatonin, pre- to post-treatment changes in sleep onset showed a significant linear relationship with pre-treatment values of DLMO (R = 0.42; p = 0.008), indicating that more delayed DLMO values at baseline associated with stronger advances of sleep onset after melatonin treatment. This relationship was not significant in placebo (R = 0.078; p = 0.645). Between-group differences in changes of DLMO were not significantly related to presence of comorbid psychiatric disorders. Urinary metabolites or temperature were not included in any of the pivotal studies.

Changes in Alertness / Fatigue / Cognition

[redacted] reported that improvement in sleep was expected to be associated with an improvement in behaviour, cognitive performance and quality of life, however once adjusted for improvements in sleep, melatonin demonstrated no effect on behaviour, cognitive performance, and quality of life.

Long-term Follow-Up

An open label follow-up period was assessed by [redacted] and by [redacted]. At 3 months follow-up [redacted]) those who continued with open-label treatment had continued to improve sleep duration ($p < .01$), but sleep-onset latency was not statistically significant different compared to the randomized melatonin treatment period. At 2 years of follow-up [redacted] , 19/24 still used melatonin (4.4 ± 2.0 mg at 7:42 PM ± 50 minutes), 1 used it occasionally, and 4 stopped after 17.23 ± 3.3 months.

Conclusions

On review of the pivotal studies it is evident that the efficacy of immediate release melatonin to improve sleep has been demonstrated in children and adolescents with chronic insomnia and ADHD. Benefits have been demonstrated on sleep onset time, sleep onset latency, advances in DLMO and increased total sleep time. Based on the totality of evidence from these pivotal studies the Applicant has proposed that Ceyesto treatment should only be initiated in patients who have had an inadequate response to sleep hygiene measures, reflecting both non-responders and patients who relapsed following use of sleep hygiene.

Melatonin treatment was effective when given every day following various treatment regimens. In order to align prescribing between indications, the Applicant suggests that melatonin should be given, 30-60 minutes before the fixed desired bedtime. The requirements for a fixed bedtime and daily dosing have been emphasised in the updated SmPC.

In the pivotal studies, efficacy was seen in the range of 3-6mg, with the 6 mg dose only given to children of higher body weight. In the supportive studies, doses as low as 0.5 mg were shown to be effective. Therefore, the proposed recommended starting dose of Ceyesto 1mg/ml Oral solution of 1-2 mg is a balance between the effective doses in the pivotal and supportive studies. It is proposed that the dose of melatonin can be increased up to a maximum 5 mg per day, independent of age. The lowest effective dose should be sought.

The dose that adequately alleviates symptoms should be taken for the shortest period. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. In patients who continue to require treatment into adulthood, melatonin may continue to be an effective treatment.

This evidence from the literature has been transcribed into the updated wording presented in section 4.2 of the proposed SmPC.

The posology in the Applicant's proposed SmPC is also broadly in line with the other approved immediate release melatonin products (tablets / oral solutions) which have been recently approved (6 since 2020) within Europe / UK for the same indication. All ten products were understood to be approved under Article 10a which fully supports the 'well-established' use of melatonin in this indication / population and the posology chosen.

Supportive Studies in ADHD

Study Designs

Five studies have been designated as supportive studies in ADHD. The studies include two reviews, a naturalistic design based on a clinical database, an open label long term follow up and one other open label study design.

[redacted] retrospectively reviewed the experience in using melatonin to treat insomnia in a large series of 107 children (aged between 2 and 18) with autism spectrum disorders, emphasizing issues related to safety and tolerability. Melatonin dose ranged from 0.75 to 6 mg. Meanwhile [redacted] undertook a systematic review of 4 studies (n=251) in ADHD children with insomnia, aged between 6 and 14, being treated with melatonin at a dose of 3 to 6 mg.

[redacted] conducted a 3-year follow-up assessment, of the [redacted]. trial to assess the relapse rate of SOI after discontinuation of melatonin and the long-term efficacy and safety of melatonin treatment. Subjects were offered extended melatonin treatment under physician care and were encouraged to discontinue treatment for at least 1 week each year to reassess treatment need. Ninety-four parents of children with ADHD and SOI who participated in the melatonin study completed a questionnaire.

[redacted] undertook a naturalistic study design based on clinical practice in children with ADHD who developed sleep problems after starting methylphenidate (MPH). The 84 patients had a mean age of 11.6 ± 2.2 years and received a melatonin dose from 1 to 5 mg. The severity of sleep disorder (sleep onset delay) was recorded at baseline and after a follow-up of at least 4 weeks using a seven-point Likert scale according to the Clinical Global Impression Severity score. Efficacy of melatonin on sleep was assessed using a Likert scale according to the Global Impression Improvement (CGI-I) score based on parents' reports.

[redacted] investigated whether melatonin could be used as a safe drug to treat insomnia problems in children with ADHD on methylphenidate medication. Baseline recordings of falling asleep time in 24 subjects before melatonin medication was reported with recordings of falling asleep time after melatonin use after 1–4 weeks in 24 subjects and after 3 months use in 13 subjects.

Sleep Onset Time or Latency

Three of the supportive studies in ADHD included endpoints related to sleep onset and all showed improvements (Table 13). [redacted] reported at a mean 3.7 years follow-up, 61 (65%) parents reported that their children were still using melatonin daily, with a mean dose of 4 mg, mean administration time of 20:00 hours, and mean duration of 18 months (range 1–57). Seventy-one percent (n = 67) of children temporarily discontinued treatment and 92% (n = 60) of those subjects experienced a delay in sleep onset. [redacted] showed an improved mean sleep onset time of 2.13±1.05 minutes whilst [redacted] showed a significantly improved sleep onset latency of 47 minutes (p = 0.012).

Total Sleep Time

Two studies assessed total sleep time with both reporting improvements compared to baseline. [redacted] reported significantly improved sleep time at 52 minutes (p =0.002) and [redacted] also reported improvements but did not specify further (Table 13).

PD Markers

The DLMO was assessed at the baseline phase by [redacted]. The authors analysed pre-treatment DLMO in the different groups of children in order to determine whether there is an association between pre-treatment DLMO and successful discontinuation of treatment

or decrease of melatonin intake. The mean (± S.E.M.) pre-treatment DLMO of the eight children who discontinued treatment completely because of improvement of sleep onset insomnia was 20:21 ± 0.25 hr, while this was 20:41 ± 0.06 hr in the remaining subjects (p = 0.413, effect size = 0.09). The mean (± S.E.M.) pre-treatment DLMO of the eleven children who used melatonin occasionally was 20:11 ± 0.15 hr against 20:48 ± 0.07 hr in the 61 children who used melatonin daily (p = 0.037). Correction for age was not applied because of an absence of between-group differences in age.

Changes in Alertness / Fatigue / Cognition

All studies recorded an improvement in alertness, fatigue, cognition and behaviour.

Conclusions

All supportive studies observed improvements in alertness, fatigue or cognition with melatonin at varying doses. In those studies assessing sleep, improvements in total sleep time and sleep onset latency were also improved. Finally, an improvement in DLMO, a PD marker, was also observed by [redacted] compared to baseline with the melatonin (3 or 6 mg) group.

In short, the supportive studies all endorse the Applicant's proposed indication and posology.

Table 12 Design of Studies of Melatonin in Paediatric Insomnia with ADHD

Stndy	N [n]/ Sex /Age	Melatonin Dose/ Formulation/ Duration	Design	Popnlation	Endpoints
PIVOTAL STUDIES IN ADHD					
[redacted]	50 (7 to 12 years)	Melatonin IR (<30kg=3 mg; >30kg= 6 mg [Nntricentnry, Canada]) + Ritalin (1mg/kg) or placebo + Ritalin (1mg/kg) x8w	R-DB-PC	Children with ADHD treated with Ritalin	Three-day food record, and standard weight and height of children were evaluated prior to the treatment and 8 weeks after the treatment. Children's appetite and sleep (sleep onset latency, total sleep time)were evalnated in weeks 0, 2, 4 and 8 nsing ADHD rating scale, SDSC, and appetite qnestionnaires
[redacted]	105 (6 to 12 years)	Melatonin IR (<40kg=3 mg, >40kg= 6mg [Pharma Nord]) or placebo at 7pm x4w +2y OLFU	R-PC-DB +OLFU	Medically referred or newly recrnited children with diagnosed ADHD with chronic sleep onset insomnia	Sleep was estimated nsing actigraphy and sleep logs. Actigraphy data were converted into sleep parameters, inclnding sleep onset, sleep latency, wake np time; total time asleep, sleep efficiency, moving time. DLMO was assessed at baseline and on the first evening of the fonrth treatment week nsing saliva samples.
[redacted]	27 (6 to 14 years)	Melatonin IR 5mg (Circa Dia BV), or placebo 20 min before bedtime. (30 d crossover: 10+5WO+10) +3M OLFU	R-PC-DB-XO +OLFU	Medically referred ADHD (Paediatric) with a mean SOL >60 minntes on ⩾30% of nights after sleep hygiene	The primary efficacy measnre was the mean SOL in each of the melatonin and placebo treatment phases as recorded on the parent-completed somnolog. Actigraph ontcome measures inclnded mean SOL, night-to-night variability in SOL, total sleep dnration, and correlation with somnologs.
SUPPORTIVE (ADHD alone)					
[redacted]	107 (age 2 to 18 years)	0.75mg to 6mg (1.8 ± 1.4 years)	Retrospective review	Insomnia with ADHD	Sleep-onset insomnia and sleep-maintenance insomnia
[redacted]	251, 6 to 14 years	3 to 6 mg prior to bedtime (10d -3m)	Systematic review	Insomnia in paediatric patients with ADHD and sleep disorders	Sleep parameters (sleep onset, total sleep time, sleep latency, DLMO) and specific core problems (anger, sleep, attention) reported by parents.
[redacted]	105 (age 6 to 12 years)	0.5-10 mg (3.7 years)	L-FU-OL-	Children with ADHD and CSOI	Parents were asked to complete a questionnaire about the long-term melatonin effects.
[redacted]	74 (mean age 11.6 ± 2.2 years)	1-5mg (4 weeks to 12 months)	Natnralistic stndy based on clinical database	Children with ADHD who developed sleep problems after starting MPH	The severity of sleep disorder (sleep onset delay) was recorded at baseline and after a follow-np of at least 4 weeks nsing a seven-point Likert scale according to the Clinical Global Impression Severity score. Efficacy of melatonin on sleep was assessed nsing a Likert scale according to the Global Impression Improvement (CGI-I) score based on parents' reports.
[redacted]	27 with new onset insomnia (age not stated)	3mg IR	OL	Children with ADHD on methylphenidate treatment	Short-term (1 – 4 week) and long-term (after 3 months) effects of melatonin on time to fall asleep, sleep onset.
SUPPORTIVE (ADHD mixed NDD)					
[redacted]	682, <18 years	0.1 mg – 12 mg (1-13 weeks)	Metanalysis (9 stndies)	Sleep problems with NDD	Total sleep time, sleep onset latency, frequency of nocturnal awakening and early-morning awakening time, parental perception of the effect of melatonin treatment on their child's behaviour, quality of life for both children and families
[redacted]	ADHD:274, Antism: 124	5mg M administered 20 minntes before bedtime	Systematic review	Sleep disorders with ADHD or Antism	sleep-onset latency, sleep onset, total sleep, and some subjective evaluations based on parental opinion of change in sleep

[redacted]	146 (3 to 15 years and 8 months)	0.5 mg, 2 mg, 6 mg and 12 mg (12 weeks) I, orally or throngh a nasogastric feeding tnbe or gastrostomy feeding tnbe.	R-C	Children with Nenrodevelopmental Disorders (NDD)	Total night-time sleep time (TST) calcnlated nsing sleep diaries, TST calcnlated nsing actigraphy data, sleep-onset latency (SOL) (time taken to fall asleep), sleep efficiency, Composite Sleep Distnrbance Index score, global measure of child's sleep qnality, Aberrant Behavionr Checklist, Family Impact Modnle of the Paediatric Qnality of Life Inventory (PedsQL™), the Epworth Sleepiness Scale, nnmber
[redacted]	45 (mean age of 6.3 ± 1.7 years)	2.5-10 mg (mean dnration of 326 days)	Prospective, observational, natnralistic study	NDD	Sleep (i.e., total sleep time, time to sleep onset and night awakenings) were assessed by parents via a structnred sleep diary for at least 2 weeks before and after the start of melatonin treatment.
[redacted]	160 (age 4 to 10 years)	3mg controlled-release melatonin alone, 3mg controlled-release melatonin + CBT, CBT alone, placebo (12 weeks)	R-PC-	Children with ASD suffering from sleep onset insomnia and impaired sleep maintenance	Sleep behaviour was assessed using the Children's Sleep Habits Questionnaire (CSHQ). Sleep-wake patterns were monitored with an actigraph, where sleep measurements inclnding SOL, total dnration of sleep (actnal sleep time, exclnding sleep latency and wakening after sleep onset), nnmber of night-wakings and WASO were collected. Parents were also asked to note specific sleep-related events on a daily basis in sleep diaries.
[redacted]	44 (age 2 to 18 years)	Initially, 5-15mg controlled-release, then changed to 5-15mg fast release (3.8yr)	Prospective follow-np stndy	Children with NDD and treatment resistant CRSD	Melatonin therapy on effectiveness parameters on a 4-point Likert scale
[redacted]	88 (age 5 to 20 years)	2-30 mg prolonged-release melatonin (6-72 months)	Long-term study	Children with NDD	A structured questionnaire for the parents, comprising a combination of multiple-choice and nnmeric questions addressing sleep onset/ offset, sleep dnration, sleep latency, sleep quality, number of awakenings, daytime napping, and mood changes.
[redacted]	20 (age 13 months to 15 years)	5mg or placebo (week 1 for baseline sleep pattern, followed by 2+1+2 weeks crossover)	R-DB-PC	Children with developmental disabilities	Primary outcome measures of sleep latency, total hours of sleep, and number of night awakenings were assessed nsing a sleep log recorded by parents.
[redacted]	7 (age 2 to 18 years)	1-5 mg (unspecified duration)	Retrospective study	Children with ASD	SOL and nocturnal awakenings
[redacted]	11 (age 4 to 16 years)	5mg or placebo (4+1+4w crossover)	R-PC-DB	Children with ASD	Sleep charts, completed by the parents inclnding total sleep time, sleep latency, night awakenings and morning awakening.
[redacted]	20 (age 2.6 to 9.1 years)	CR melatonin 3mg (24 months)	OL	Children with ASD	Primary efficacy measnres included changes in total score over time on the CSHQ (Children's Sleep Habits Qnestionnaire). Secondary efficacy measures inclnded change from baseline to stndy endpoint as assessed by the analysis of sleep diaries (bedtime, risetime, sleep length, wake after sleep onset, bedtime irregularity and co-sleeping).
[redacted]	9 (age 3 to 8 years)	1-3mg (17 weeks)	OL	Children with ASD	Sleep parameters (sleep onset latency, wake-after-sleep-onset (WASO), sleep efficiency, sleep duration) were compnted nsing wrist actigraphy and overnight PSG, serial blood draws at baseline and at each dose of supplemental melatonin to measure DLMO and PK parameters for snpplemental melatonin. The stndy also collected parent-reported assessments nsing the Children's Sleep Habits Questionnaire (CSHQ), sleep histories, and sleep diaries to measure discrete night wakings
[redacted]	146 (age 3 to 15 years and 8 months)	0.5 mg, 2 mg, 6 mg and 12 mg (12 weeks)	R-PC-DB	Children with NDD	Total sleep time at night after 12 weeks adjusted for baseline recorded in sleep diaries completed by the parent. Secondary ontcomes inclnded sleep onset latency, assessments of child behavionr, family functioning, and adverse events. Sleep was measured with diaries and actigraphy.

[redacted]	42 (age 4 to 21 years) 16 in the crossover part	2-12 mg fast release and controlled-release melatonin	R-PC-DB	Children with sleep-wake cycle disorders and severe nenrodevelopmental difficnlties	The effectiveness of treatment was assessed by sleep charts and clinical follow-np. Emphasis was placed on the jndgement of the parents, who had gnidance from the physicians.
[redacted]	24 (age 3 to 10 years)	1 to 6 mg titration (17 weeks)	OL	Children with ASD	Sleep latency measured by actigraphy, and daily sleep diaries completed by parents to assist in interpretation of actigraphy data.
[redacted]	35 (age 1 to 17 years)	0.5–7.5 mg (4-10 weeks)	Systematic review	Paediatric Nenrodevelopmental Disabilities	All three studies used sleep diaries completed by carers to record information. One study (McArthnr and Bndden 1998) also nsed wrist actigraphy to monitor sleep–wake activity. Ontcome data on specified ontcomes (total sleep time, sleep latency, nnmber of awakenings, and parental view of effect) were available for all three stndies, apart from sleep latency in one stndy (Camfield et al. 1996), and parental view in another (McArthnr and Budden 1998).
[redacted]	6 (age 9 months to 18 years)	5 mg orally or via gastrostomy tnbe at the patient's habitnal bedtime (treatment duration not stated)	NA	Children with multiple nenrological deficits	Post-treatment data elucidated changes in sleep-onset latency, number of nocturnal wakings, length of noctnrnal waking, and total sleep time.
[redacted]	33 (age 10 to 18 years)	3-5 mg (6m)	Retrospective study	DSPS adolescents with ADHD/OSAS	Sleep onset and duration is assessed by actigraphic/sleep log data.
[redacted]	72 (age 6 to 12 years)	3 mg or 6mg M compared with placebo for 4 weeks	Meta-analysis of 9 RCTs	DSPS or insomnia+ADHD	Sleep was assessed with log and actigraphy during this week and the week before. Ontcomes were the shifts in DLMO, SO, and SOL. Participants were instructed to wear an actigraph whereby the data were nsed to calculate SO, wake-up time, SOL and TST
[redacted]	16 (age 5 to 13 years)	0.1-12mg (length of treatment: 1 month – 5 years)	Qnalitative exploratory study	Children with NDD	30–90 minnte interviews were conducted with parents.
[redacted]	50 31M: 19F 2–18y	5-15mg SR (Circa Dia BV hospital formnlated) x10d +OLx3m	R-PC-DB-XO +OLFU	DSPS or ISM confirmed dnring baseline + NDD	Primary: somnolog TST. SOL, SE, longest sleep episode and nnmber of night-time wakings, CGI, vital signs, physical examination, AE.
[redacted]	18 (age 2 to 15.25 years)	3 mg or placebo (2w+2w)	R-PC-DB	Paediatric ASD, fragile X syndrome	Sleep variables, inclnding sleep dnration, sleep-onset time, sleep-onset latency time and nnmber of night awakenings were recorded nsing an Actiwatch and from sleep diaries completed by parents.
[redacted]	22 (age 4 to 16 years)	10mg or placebo (3m + 3m crossover)	R-PC-DB	Paediatric ASD	Changes in sleep patterns were assessed using sleep diaries, which were completed daily by parents. The diaries docnmented start of bedtime rontine, time the capsule was taken, times asleep, night wakenings and times awake. Primary ontcome measures were sleep latency, total sleep time and nnmber of wakenings. Fnrther aspects of sleep, health and behavionr were assessed using the SDQ, DBC and GHQ.
[redacted]	99 (age 6 to 15 years)	1,2, or 4 mg (26 weeks)	OL	Paediatric NDD	Variables of sleep included sleep onset latency (primary endpoint) were recorded with electronic sleep diary. Aberrant behaviours were investigated with ABC-J.

ABC-J= aberrant behavior checklist-Japanese version, AE=adverse events, CGI= Clinical global impression, CSHQ= Children's sleep habits questionnaire, DBC= Developmental behaviour checklist, DLMO= Dim light melatonin onset, DSPS= Delayed Sleep Phase Syndrome, GHQ= General health questionnaire, ISM=impaired sleep maintenance , IR=Immediate-release, NDD= Neuro-developmental Disabilities, SDQ= Sleep difficulties questionnaire, SDSC= Sleep disturbance score for children, SE=Sleep efficiency, SOL= Sleep Onset Latency, SOT=Sleep onset time, SR=sustained release, TST=total sleep time, WASO= Wakefulness after sleep onset, WT=wake time

Table 13 Efficacy of Melatonin in Paediatric Chronic with ADHD

Stndy	N [n]/ Sex /Age	Arm or Epoch	Alertness/fatigne/ cognition/behavionr	Change from baseline					
				Sleep onset time/latency	Wake time	Total sleep time	Temperatnre	DLMO	UaMT6s
PIVOTAL STUDIES IN ADHD									
[redacted]	50 (age 7 to 12 years)	Melatonin (3 or 6 mg) + Ritalin (1mg/kg) (8 weeks)	ND	SOL at baseline:23.15 ± 15.25 min SOL at 8w: 17.96 ± 11.66 min (p=0.047)	total sleep distnrbance score (48.84±13.42 vs. 41.30±9.67; p=0.000)	8.00h to 8.51h (p=0.06)	ND	ND	ND
		placebo + Ritalin (1mg/kg) (8 weeks)		no significant change	no significant change	8.77h to 8.27h no significant change			
[redacted]	105 (age 6 to 12 years)	3 mg or 6mg M compared with placebo for 4 weeks	Not significantly improved once adjnsted for sleep-related scores.	SOT Advanced by 26.9 +/- 47.8 minntes (p < .0001 vs placebo	increased sleep efficiency (p=.01), decreased noctnmal restlessness (L5; p = .03) compared to placebo	19.8 ± 61.9 minntes (p = .01 vs placebo)	ND	Advanced by 44.4 +/- 67.9 minntes (p < .0001 vs placebo)	ND
		Placebo		SOT delayed by 10.5 +/- 37.4 minntes		13.6 ± 50.6 minntes	ND	Delayed by12.8 +/- 60.0 minntes	ND
[redacted]	27 (age 6 to 14 years)	5mg (30 d crossover)	ND	46.4 minntes	NR	NR	ND	ND	ND
		Placebo		62.1 minutes	NR	NR	ND	ND	ND
SUPPORTIVE STUDIES IN ADHD									
[redacted]	107 (age 2 to 18 years)	0.75mg to 6mg (1.8 ± 1.4 years)	Improved	NR	NR	NR	ND	ND	ND
[redacted]	251, 6 to 14 years	3 to 6 mg prior to bedtime (10d -3m) (4 studies) and Placebo	Improved	P-M: 47 minntes, p = 0.012	NR	P-M: 52 minntes, p =0.002	ND	[redacted]	ND
[redacted]	105 (age 6 to 12 years)	0.5-10 mg (3.7 years)	Improved	ND	ND	ND	ND	20:48 ± 0.07 hr (p = 0.037, ES = 0.26).	ND
[redacted]	74 (mean age 11.6 ± 2.2 years)	1-5mg (4 weeks to 12 months)	Improved	2.13±1.05 minntes	NR	NR	ND	ND	ND
	24 with new onset insomnia (age not stated)	Not stated							
[redacted]	27, with new onset insomnia	3mg IR	Improved	135 min (median increase)	ND	15–64 min	ND	ND	ND

Stndy	N [n]/ Sex /Age	Arm or Epoch	Alertness/fatigne/ cognition/behavionr	Change from baseline					
				Sleep onset time/latency	Wake time	Total sleep time	Temperatnre	DLMO	UaMT6s
	(age not stated)								
SUPPORTIVE STUDIES IN MIXED NDD									
[redacted]	146 (3 to 15 years and 8 months)	0.5 mg, 2 mg, 6 mg and 12 mg (12 weeks) IR	Improved	P-M: –37.49 minntes (95% CI –55.27 to –19.71 minntes; p < 0.0001)	NR	P-M: 22.43 minntes [95% confidence interval (CI) 0.52 to 44.34 minntes; p = 0.04]	ND	Reported*	ND
		Placebo	Improved		NR		ND	NR	ND
[redacted]	682, <18 years	0.1 mg – 12 mg (1-13 weeks)	Improved	28.97, (95% CI -39.78 to -18.17)	ND	48.26 minutes, 95% CI 36.79 to 59.73	ND	ND	ND
[redacted]	ADHD:274, Antism: 124	5mg M administered 20 minntes before bedtime	Improved	Varions	Varions	Varions	ND	ND	ND
[redacted]	45 (mean age of 6.3 ± 1.7 years)	2.5-10 mg and placebo (mean dnration of 326 days)	Improved	P-M: -1.25 ± 1.13 h	PM: -0.38 ± 0.47	P-M: 1.93 ± 1.41 h	ND	ND	ND
[redacted]	160 (age 4 to 10 years)	3mg controlled-release melatonin alone, 3mg controlled-release melatonin + CBT, CBT alone, Placebo (12 weeks)	Decreased	<30 min	NR	NR	ND	ND	ND
[redacted]	44 (age 2 to 18 years)	Initially, 5-15mg controlled-release, then changed to 5-15mg fast release (3.8yr)	Improved	NR	NR	NR	ND	ND	ND
[redacted]	88 (age 5 to 20 years)	2-30 mg prolonged-release melatonin (6-72 months)	Improved	44.0% (p < 0.001)	75% (p < 0.001),	Improved by 81.9%	ND	ND	ND
[redacted]	20 (age 13 months to 15 years)	5mg or placebo (week 1 for baseline sleep pattern, followed by 2+1+2 weeks crossover)	Decreased	0.7 hr (SD:0.8)	0.9 (0.7)	8.1 hr (1.6)	ND	ND	ND
		Placebo	Decreased	NR	NR	NR	ND	ND	ND
[redacted]	7 (age 2 to 18 years)	1-5 mg (unspecified duration)	Improved	NR	NR	NR	ND	ND	ND
[redacted]	11 (age 4 to 16 years)	5mg or placebo (4+1+4w crossover)	Improved	1.06 h (95% CI 0.98-1.1.3)	0.08 h (95% CI 0.04-0.12)	9.84 h (95% CI 9.68-9.99)	ND	ND	ND
[redacted]	20 (age 2.6 to 9.1 years)	CR melatonin 3mg (24 months)	Improved	NR	NR	NR	ND	ND	ND

Stndy	N [n]/ Sex /Age	Arm or Epoch	Alertness/fatigne/ cognition/behavionr	Change from baseline					
				Sleep onset time/latency	Wake time	Total sleep time	Temperatnre	DLMO	UaMT6s
[redacted]	9 (age 3 to 8 years)	1-3mg (17 weeks)	Improved	26.6 (10.2)	NR	NR	ND	ND	ND
[redacted]	146 (age 3 to 15 years and 8 months)	0.5 mg, 2 mg, 6 mg and 12 mg (12 weeks)	Improved	-37.5 minntes, -55.3 to -19.7 minntes, p<0.001	29.9 minntes, 13.6 to 46.3 minntes	22.4 minutes (95% CI 0.5 to 44.3 minntes, p=0.04)	ND	ND	ND
[redacted]	42 (age 4 to 21 years) 16 in the crossover part	2-12 mg fast release and controlled-release melatonin	Improved	Improved (NR)	ND	ND	ND	ND	ND
[redacted]	24 (age 3 to 10 years)	1 to 6 mg titration (17 weeks)	Improved	22.5 minntes	68.6 minntes	457.3 minntes	ND	ND	ND
[redacted]	35 (age 1 to 17 years)	0.5–7.5 mg (4-10 weeks)	Improved	Varions	Varions	Varions	ND	ND	ND
[redacted]	6 (age 9 months to 18 years)	5 mg orally or via gastrostomy tnbe at the patient's habitnal bedtime (treatment dnration not stated)	Improved	NR	NR	NR	ND	ND	ND
[redacted]	33 (age 10 to 18 years)	3-5 mg (6m)	Improved	02:00±01:30 (before treatment) and 03:42±02:00 (after treatment)	NR	NR	ND	ND	ND
[redacted]	72 (age 6 to 12 years)	3 mg or 6mg M compared with placebo for 4 weeks	Improved	Advanced by 0.64 honrs	0.16 h	by 16.04 min	ND	1.13 honrs	ND
[redacted]	16 (age 5 to 13 years)	0.1-12mg (length of treatment: 1 month – 5 years)	Improved	NR	NR	NR	ND	ND	ND
[redacted]	50 31M: 19F 2–18y	5-15mg SR (Circa Dia BV hospital formnlated) x10d +OLx3m	Improved	P-M: 32.48 min	NR	P-M: 31 min	ND	ND	ND
[redacted]	18 (age 2 to 15.25 years)	3 mg or placebo (2w+2w)	Improved	P-M: 28 minntes (p = 0.0001)	NR	P-M: 42 minntes (p = 0.02).	ND	ND	ND
[redacted]	22 (age 4 to 16 years)	10mg or placebo (3m + 3m crossover)	Improved	P-M: 47 minntes, p = 0.012	NR	P-M: 52 minntes, p =0.002	ND	ND	ND
[redacted]	99 (age 6 to 15 years)	1,2, or 4 mg (26 weeks)	Improved	36.7 ± 46.1 min; 95% CI, - 45.9 to - 27.5; P < 0.0001	NR	NR	ND	ND	ND

* In exploratory analyses the authors have found a strong correlation between those children with later DLMO peaks and those children who fall asleep later

Summary Across Pivotal and Supportive Studies in ADHD and mixed populations with NDD including ADHD

The Applicant designated studies in mixed populations including both patients with ADHD and those with other comorbidities such as autism, learning disabilities, intellectual disability (also known as mental retardation), conduct disorders, cerebral palsy, and impairments in vision and hearing as supportive studies. The overall results across the pivotal and supportive studies in ADHD and the supportive studies in NDD are described here.

For insomnia in children with NDD, a targeted literature search was conducted as described in Module 2.7.3. Studies were rejected if they were duplicates, A sequential review of the titles and abstracts was performed, and studies were included if they were: reported in English; reporting a clinical study, meta-analysis or systematic review; using an oral formulation of melatonin and performed in the specific indication targeted by the search.

Ninety-one publications reporting paediatric studies of melatonin on sleep with more than 7000 records were identified by the literature search (Module 2.7.3). Once reviews were eliminated more than 80 publications in >3500 children remained, including 4 large scale randomised control trials (RCT) that each included ⩾100 participants. The causes of disturbed sleep included primary insomnia, delayed phase sleep syndrome/delayed sleep phase disorder (DSPS/DSPD), neurodevelopmental disorders including ASD and epilepsy, atopic dermatitis, cystic fibrosis and blindness. All publications which used high quality synthetic melatonin together with the currently recommended posology of melatonin reported positive effects on sleep, although the effect size varied between studies. The most beneficial effects were obtained when melatonin was combined with measures to promote good sleep hygiene, and the most consistent effects were seen in reducing the time to sleep onset.

Of these, 39 studies included children and adolescents with neurodevelopmental disorders including ASD and ADHD. In the original submission, 20 were considered as pivotal and 19 as supportive studies. Of these studies, 17 studies were prospective RCTs, 4 systematic reviews, 1 meta-analysis, 6 open-label, and remaining studies were either long term follow-up or naturalistic or retrospective review studies. Participants were children and adolescents below 18 years of age who had both neurodevelopmental and sleep disorders, however, 3 studies also included children aged 8 months to 2 years as the starting age in their studies. The enrolled children were described in the primary studies to have the following neurodevelopmental disabilities: neurodevelopmental disorder, autistic spectrum disorders, and ADHD. Sleep data were recorded either by using sleep diaries (four studies), using actigraph or polysomnography (one study), or using both sleep diary and actigraph (eight studies). The melatonin used was immediate release in fast-release melatonin in 10 studies, and 2 studies used a combination of the slow and fast melatonin preparations. One further study used slow-release melatonin. The dosages used ranged from 0.1 to 12mg. Escalating dose of melatonin according to response was used in three of the included studies. The duration of melatonin treatment ranged from 1 to 13 weeks. The primary and secondary endpoints majorly included in these studies was total sleep time (TST) calculated using actigraphy data, sleep-onset latency (SOL) (time taken to fall asleep), sleep efficiency. In almost all studies, the results determined that in children with neurodevelopmental disorders and sleep problems, immediate release melatonin was found to be more effective than placebo in increasing total sleep time and reducing sleep onset latency.

Parent directed behavioural sleep interventions (BSI) should always be the first line approach when treating insomnia in children, and can be delivered in many flexible and cost-effective

ways [redacted] Parents can implement these strategies to help their child 'learn' healthy sleep behaviours and, if necessary, "unlearn" inappropriate sleep behaviours. BSIs have well demonstrated efficacy in randomised controlled trials for younger typically developing (TD) children, and older (up to 12 years of age) autism and attention-deficit hyperactivity disorder (ADHD) populations [redacted] and can be as effective as medications, but with more long-term benefits and without adverse effects [redacted]

The pivotal and supportive studies in a homogenous population of children with ADHD are described in the section above. Pertinent findings from specific studies in children with mixed NDD are described below and in Table 12 and Table 13.

Melatonin treatment was effective in a RCT by [redacted] Melatonin affects were studied in combination with cognitive–behavioural therapy in children (aged from 4 to 10 years) with autistic spectrum disorders with sleep onset insomnia and impaired sleep maintenance. Participants assigned to the melatonin group were given orally a 3 - mg controlled - release (CR) dose of melatonin and administered at approximately 21:00h. Participants in the combined cognitive–behavioural therapy (CBT) and melatonin group received both melatonin and CBT. Children who received the active treatment were able to maintain sleep more efficiently than those in the placebo group. However, of the three active treatments, melatonin in combination with CBT was the most effective in reducing insomnia symptoms, followed by the melatonin (MLT) alone and then the CBT group compared to the placebo group. reducing insomnia symptoms (including bedtime resistance, sleep onset delay, night-wakings and sleep duration subscales), while cognitive-behavioural therapy had a light positive impact mainly on sleep latency, suggesting that some behavioural aspects might play a role in determining initial insomnia. The combination treatment group showed a trend to outperform other active treatment groups, with fewer dropouts and a greater proportion of treatment responders achieving clinically significant changes (63.38% normative sleep efficiency criterion of >85% and 84.62%, sleep onset latency <30 min).

Seventeen autistic children completed a randomized, double-blind, cross-over trial of melatonin versus placebo control over a period of 6 months, with interventions consisting of melatonin 2 mg or placebo administered before a scheduled bedtime [redacted]. Melatonin significantly improved sleep-onset latency (mean: 47 minutes, p = .012) and total sleep (mean: 52 minutes, p = .002) compared to placebo, but the number of night awakenings did not differ. The mean final dose when on the melatonin arm was 7 mg and ranged from 2 to 10 mg. The side effect incidence was low and not significantly different between the 2 arms.

Another study aimed to describe the authors' experience with melatonin for the treatment of insomnia in 107 children, emphasizing issues related to safety and tolerability [redacted]. The majority of parents reported improvement in their child's sleep (60%) at the first follow-up visit. Parents of 27 (25%) children no longer reported sleep concerns at follow-up visits after initiation of melatonin. In 7 children, melatonin was reported by parents to initially improve sleep, but sleep problems returned after 3 to 12 months, despite dose escalation. Forty-seven children were started on melatonin at doses of less than 3 mg. In these children, 19 required a dose increase to 3 mg for effect on sleep. Twenty-four children were started on 3 mg, and 1 child required a dose increase to 6 mg for effect on sleep, whereas 1 child required a dose decrease to 1.5 mg due to reported grogginess. Seven children were started on doses above 3 mg; of these, 3 children had their doses decreased to 1.5 to 3 mg with continued improvement in sleep. The majority of children were started taking

immediate-release melatonin (melatonin IR), with only 10 started on an extended-release formulation.

[redacted] examined a liquid formulation of supplemental melatonin for sleep in 46 children with autism in an open-label dose escalation study. The authors' goal was to determine the lowest possible dose that was effective and tolerable. Children were initially given 1 mg of melatonin for 3 weeks. Dependent on response, the dose would either remain the same or increase in increments of 3 mg for 3 weeks. A satisfactory response in sleep latency within the 1 and 3 mg dosing period was achieved in the first week. However, duration of sleep, wake time after sleep onset, and sleep efficiency were not significantly different with melatonin. The medication was tolerated well with minimal adverse effects and an improvement in the children's behaviour was seen as well.

A systematic review and meta-analysis performed in children with autism spectrum disease evaluated 35 studies [redacted] The authors found that melatonin use significantly improved sleep duration and sleep-onset latency and improved daytime behaviour but did not affect night-time awakenings. Furthermore, the side effects were minimal to none.

Sleep Onset latency (SOL)

Sleep onset latency was measured in thirteen systematic reviews and showed improvements in the melatonin groups. Of the thirteen systematic reviews identified, six were in the paediatric population [redacted]

A significant decrease in time to sleep onset ($p<0.05$) where melatonin was compared with a placebo in two studies was reported in [redacted] after reviewing available evidence from 3 randomized studies in children with neurodevelopmental disabilities.

Six out of seven trials involving 387 children and adolescents with sleep onset insomnia reviewed in [redacted] reported that melatonin decreased sleep onset latency ($p < 0.00001$).

A statistically significant decrease (favouring melatonin) in sleep onset latency ($p<0.001$) was found by [redacted] after a review of studies reporting on children with neurodisabilities suffering from non-respiratory sleep disturbances (n=583).

[redacted] reviewed 7 studies in special paediatric populations (behaviour disorders, autism, idiopathic insomnia, atopic dermatitis, epilepsy and developmental disabilities; total n=233) and reported that each study showed an improvement in sleep-onset latency after melatonin supplementation. Significantly improved sleep onset latency was reported in eleven studies reviewed in [redacted] (n=581). A review of 4 studies (n=251) in ADHD children with insomnia [redacted] showed a significantly improved sleep onset latency.

Four reviews where sleep onset latency was measured were in mixed population [redacted].

[redacted] reviewed 11 studies (n=174) on melatonin and sleep disorders associated with intellectual disability (ID) and concluded that melatonin is particularly effective in improving time to get to sleep in children and adolescents with ID and probably has a similar effect on adults.

A significant benefit of melatonin in reducing sleep latency was reported in [redacted] where 19 studies (n=1683) reviewed this sleep parameter in adults and children diagnosed with primary sleep disorder and reported that subjects randomly assigned to melatonin fell asleep seven minutes earlier on average than subjects receiving placebo.

[redacted] reviewed 9 trials including 91 adults and 226 children where a statistically significant decrease of sleep onset latency in children was reported.

An improvement in total sleep time was reported in three studies (n=35) included in [redacted]

A review of 4 studies (n=251) in ADHD children with insomnia [redacted] reported that most studies have shown improvements in total sleep time.

Dim light melatonin onset (DLMO)

The DLMO was assessed at the baseline phase of the randomised, double blind, placebo-controlled trial on melatonin efficacy in a study by [redacted]. The authors analysed pre-treatment DLMO in the different groups of children in order to determine whether there is an association between pre-treatment DLMO and successful discontinuation of treatment or decrease of melatonin intake. The mean (± S.E.M.) pre-treatment DLMO of the eight children who discontinued treatment completely because of improvement of sleep onset insomnia was 20:21 ± 0.25 hr, while this was 20:41 ± 0.06 hr in the remaining subjects ($p = 0.413$, effect size =)0.09). The mean (± S.E.M.) pre-treatment DLMO of the eleven children who used melatonin occasionally was 20:11 ± 0.15 hr against 20:48 ± 0.07 hr in the 61 children who used melatonin daily ($p = 0.037$, ES =)0.26). Correction for age was not applied because of an absence of between-group differences in age.

In an exploratory analysis that was conducted in a study by [redacted] authors have found a strong correlation between those children with later DLMO peaks and those children who fall asleep later. The authors also found that the amplitude of treatment response is strongly correlated with the initial severity of the sleep disorder. Thus, as has been described in typically developing children, but not replicated in this population, children who have later DLMO times fall asleep later and respond better to exogenous melatonin. As SOL and sleep duration are related, so an improvement in SOL may also lengthen sleep duration, but this depends on whether or not sleep offset (the time that the child wakes up) alters. This does, however, support the possible utility of pre-treatment DLMO measurement to predict the better treatment responders.

In a study by [redacted] melatonin-treated children showed an advance in DLMO of 44.4 ± 67.9 minutes compared with a delay of 12.8 ± 60.0 minutes in children receiving placebo ($p < 0.0001$). In melatonin, pre- to post treatment changes in sleep onset showed a significant linear relationship with pre-treatment values of DLMO ($R = 0.42$; $p = 0.008$), indicating that more delayed DLMO values at baseline associated with stronger advances of sleep onset after melatonin treatment. This relationship was not significant in placebo ($R = 0.078$; $p = 0.645$). In melatonin, pre- to post treatment changes in DLMO were not significantly related with pre- to posttreatment changes in sleep onset ($R = 0.30$; $p = 0.124$). Between-group differences in changes of DLMO were not significantly related to presence of comorbid psychiatric disorders.

<u>Systematics reviews</u>

Dim Light Melatonin Onset (DLMO) was reported in three systematic reviews [redacted] Significantly advanced DLMO in the melatonin group was reported in 1 out of 4 studies (n=105) [redacted]. DLMO was significantly advanced in the melatonin group in five out of seven studies [redacted].

Conclusions

It is evident from these supportive studies also that the Applicants proposed indication in chronic insomnia in children and adolescents with ADHD and the proposed posology has demonstrated efficacy of immediate release melatonin to improve sleep.

UK Clinical Practice and NHS Guidance Documents for Insomnia in ADHD

The Applicant has also considered the dosing in clinical practice in the UK to validate the proposed posology for Ceyesto 1mg/ml solution.

The usual dose indicated in clinical practice in NHS guidance is 2-3 mg which may be increased to 4-6mg after one to two weeks. Upper maximum doses may be as high as 10-12mg but this is rarely seen. Initiation of melatonin is usually by hospital specialists (paediatricians).

In addition, the [redacted] provides dose information for using oral melatonin in children. It states that children (1 month to 18 years old) should start off at a dose of 2–3 mg daily before bedtime and increase, if necessary, after 1–2 weeks to 4–6 mg daily, up to a maximum of 10 mg daily [redacted]. This is broadly in line with the NICE recommendation for melatonin in its ADHD guidance which commented that the RCTs in children with ADHD use doses of between 3 mg and 6 mg daily. [redacted].

It is evident that immediate release melatonin has been used for a number of years in the proposed indication and that the Applicant's proposed posology is broadly in line with that included in various NHS guidance documents. This provides further support to the Applicant's proposed posology which has been generated from review of the literature.

Safety in ADHD and NDD

In the paediatric population there were 4 large scale RCTs [redacted] that each included ⩾100 participants and the safety reporting is summarised in Module 2.7.4.

Supportive Studies in ADHD and in Mixed NDD are discussed in Module 2.7.3 and 2.7.4.

Overall Conclusion in ADHD

In the clinical literature, melatonin advanced sleep onset by 26.9 ± 47.8 minutes, compared to a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$) in a 4-week randomised, double-blind, placebo- controlled study conducted in 105 stimulant-free children of 6 to 12 years, with ADHD and chronic sleep onset insomnia [redacted] In the melatonin group an advance of sleep onset >30 minutes was more common (48.8% of children) than in those who received melatonin (12.8%, $p = 0.001$). There was an increase in mean total time asleep of 19.8 ± 61.9 minutes with melatonin and a decrease of 13.6 ± 50.6 minutes with placebo ($p = 0.01$). As compared with placebo, the melatonin group showed a decrease in sleep latency ($p = 0.001$) and increase in sleep efficiency ($p = 0.01$). The mean score on sleep log item difficulty falling asleep decreased by 1.2 ± 1.3 points (35.3% of baseline) with melatonin and by 0.1 ± 0.8 points (4.3% of baseline) with placebo ($p < 0.0001$). There was no significant effect on behaviour, cognition, and quality of life.

From a critical appraisal of the review of the peer-reviewed literature which designated pivotal and supportive studies, it can be concluded that melatonin is a safe and effective treatment for insomnia in children and adolescents presenting with ADHD. Melatonin has

demonstrated PD effects (DLMO) that can be anticipated to be of clinical value in improving insomnia and has shown positive impacts on parameters such as sleep onset latency and total sleep time. In addition, all studies recorded an improvement in alertness, fatigue, cognition and behaviour compared to baseline. Melatonin was seen to be generally well tolerated with headaches and dizziness most commonly reported.

The posology including dose / dose duration proposed by the Applicant is considered fully supported by the studies in the literature and / or established clinical practice in the UK / Europe.

The posology in the Applicant's proposed SmPC is also broadly in line with the other approved immediate release melatonin products (tablets / oral solutions) which have been recently approved (10 since 2020) within Europe / UK for the same indication. All ten products were understood to have been approved under Article 10a which fully supports the 'well-established' use of melatonin in this indication / population, the posology chosen and the consistency of the review and assessment of the available literature and clinical guidance.

In summary, based on the analysis of the peer-reviewed literature on the current knowledge on efficacy and safety of melatonin, the benefit/risk ratio of melatonin is considered to be positive. Therefore, Melatonin 1mg/ml oral solution can be recommended for the treatment of insomnia in children and adolescents (6-17 years) presenting with ADHD where sleep hygiene measures have been insufficient. In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood.

4.3 Sedation in Children and Adolescents to Facilitate EEG

General Consideration for Sedation in Children and Adolescents

Melatonin is widely used in clinical practice in the UK and worldwide for sedation prior to diagnostic procedures such as EEG, MRI and ABR. It is also being investigated by the clinical community for use prior to minor procedures such as phlebotomy or venepuncture; and as an adjunct to general anaesthesia. The distribution and availability of the clinical literature and studies reflects the long history of use of melatonin as a sedative, including retrospective studies from centres that switched their routine clinical use to melatonin from older sedatives. Randomised controlled studies are more frequently seen for newer applications of the sedative effect of melatonin such as its use as an adjunct to general anaesthesia. However, the well-established use of melatonin as a sedative is most clearly documented when it is used to facilitate EEG recording. All paediatric studies of melatonin as a sedative are presented in Module 2.7, but this clinical overview focuses on EEG studies.

Categorisation of Studies and Choice of Pivotal Study

The criteria for selecting a pivotal study and supportive studies were driven by the principles from the EMA Guideline on medicinal products for the treatment of insomnia (EMA/CHMP/16274/2009 Rev. 1, 2011) which is considered relevant for sedation considered as sleep initiation.

The systematic literature review identified 34 publications reporting use of melatonin in more than 3000 children for paediatric sedation across the last 2 decades. Indications included sedation for EEG, ABR, MRI, phlebotomy or intubation, with further studies using melatonin as a premedication before induction of general anaesthesia. The studies discussed here are the 12 studies which asseesed the use of melatonin to facilitate EEG recording. These studies were categorised into pivotal, supportive or other, as presented in Table 15.

Active comparators included midazolam, chloral hydrate, clonidine, tricolofis, or standard of care. The choice of an appropriate comparator for melatonin is limited by the number of oral drugs suitable for use in this indication and in particular since there is no current licensed product for the proposed indication in the UK. Chloral hydrate is widely used as a sleep-inducing agent around the world due to its minimal influence on EEG and is therefore considered a suitable comparator. Triclofos sodium which is the comparator used in [redacted] is a monophosphate sodium salt of trichloroethanol (i.e. the pharmacologically active metabolite of chloral hydrate). It has better palatability, less gastric irritation but more prolonged sedation as compared to chloral hydrate but is considered a suitable comparator for assessing the effectiveness of melatonin in the proposed indication. Midazolam is also used in surgical procedures in both oral and non-oral forms and is included in current NICE Guidelines along with chloral hydrate for use in sedation for painless imaging procedures [redacted] However, midazolam as a benzodiazepine is associated with risk of serious side effects and should only be administered under the direct supervision of personnel experienced in the use of benzodiazepines with adequate training in anaesthesia and airway management. Midazolam is also frequently used in epileptic children where its oromucosal formulation is indicated at doses between 2.5 and 10 mg for the treatment of prolonged, acute, convulsive seizures in children aged 3 months to < 18 years. However the level of sedation that can be achieved without affecting the EEG is limited [redacted] It is considered a suitable comparator for this indication bearing in mind the limitations already expressed above. Other alternative products are rarely used. The BNF suggests that some anxious patients may benefit from the use of hypnotics during dental procedures such as temazepam or diazepam. Temazepam is preferred when it is important to minimise any residual effect the following day. However these are not the medications of choice in sleep EEG. In practice most clinics conducting sleep EEG use melatonin in patients where a hypnotic / sedative is likely to increase the probablility of a successful recording.

Based on review of the design / results, the Applicant is designating [redacted] as the pivotal study supported specifically by [redacted] and [redacted] but also by the remaining controlled and uncontrolled publications.

[redacted] is a randomised, active-controlled parallel group study which is single blind, and was conducted in 114 children in each group with an age range of 6 months to 18 years. This study has been designated as pivotal because it is a recent, large-scale, parallel group study. The children had received sleep deprivation the night before and the primary outcome measure was successful EEG recording of at least 30 minutes. Successful completion of the sleep EEG was achieved in a similar proportion of subjects with both melatonin and triclofos, with similar results for the other parameters (Table 14).

There were 8 supportive studies using either active or placebo controls to assess sedation with melatonin to facilitate EEG recording in the paediatric population. These studies included 2489 children aged between 1 month and 18 years. A further 3 uncontrolled studies enrolled 480 children aged from 6 months to 16 years.

[redacted]

[redacted]

Efficacy Evaluation in Clinical Studies

Melatonin was effective in ensuring that the sleep EEG can be completed (primary end-point) [redacted] (Table 14).

In [redacted], the proportion of successful EEGs was similar for both groups (Melatonin 89.4%, Triclofos 91.2%). The first dose was effective in a similar percentage of children (Melatonin: 64%, Triclofos 63.15%). An augmentation dose was needed in 25.4% for Melatonin and 28% for Triclofos. Mean total sleep duration was 80 min after Melatonin and 82.39 after Triclofos administration. Adverse effects were observed in 6.14% of Melatonin and 8.65% of Triclofos group. In the Melatonin group, adverse effects- were drowsiness, headache and irritability. There was no significant difference between efficacy and tolerability of Melatonin and Triclofos. Melatonin can be safely used to achieve sleep for EEG in children and in a companion paper [redacted] Melatonin was preferred due to is better cost-effectiveness ratio (cost-effectiveness ratio [CER]-1: 18.45 vs 26.66 and CER-2 37.64 vs 63.01).

In [redacted] sleep onset latency was similar (median values melatonin 45 min, chloral hydrate 35 min, Mann-Whitney test, p=0.113). Sleep duration (median values melatonin 30 min, chloral hydrate 60 min, Mann-Whitney test, p<0.0001) and drowsiness time were significantly shorter with melatonin (median values melatonin 20 min, chloral hydrate 60 min, Mann-Whitney test, p<0.0001) which the authors considered an advantage. A second dose was required for 20 patients in the melatonin group and 6 patients in the chloral hydrate group. Few adverse drug effects were recorded in both groups.

In [redacted] the prespecified primary composite endpoint of adequate sedation (Ramsay sedation score of 4) with recording of EEG was achieved in 36.7% of midazolam group and in 73.3% of melatonin group, (p = 0.004). Time from drug administration to being adequately sedated (in minutes) was 24.1 ± 9.6 for melatonin and 18.63 ± 10.51 for midazolam (P=0.1). The Ramsay sedation score of four was obtained in all children who achieved adequate sedation 40 minutes after taking the drugs. Transient agitation was seen in 6.6% of midazolam group. No significant difference was observed from the viewpoint of side effects frequency between the two drugs, (p = 0.15).

In all clinical studies (Table 15), melatonin was at least as effective as the comparators (tricolfos, chloral hydrate, midazolam). Melatonin combined with sleep deprivation was superior to melatonin alone and to sleep deprivation alone. Melatonin was considered to provide a more appropriate duration of sleep, and had a better safety profile.

Therefore, the pivotal, supportive and other studies support the proposed indication.

Table 14: Efficacy in Pivotal and Key Supportive Studies in Sedation

Study	N / Age	Success (completion) of sleep EEG	Time to sleep onset (SOL)	Duration of sleep	Comments
PIVOTAL STUDY					
[redacted]	228 / 6m to 18y	M: 89.4% T: 91.2%	M: 39.1 min (dose 1) & 30 min (from augmentation) T: 41.6 min (dose 1) & 41.6 min (from augmentation)	M: 80 min T: 82 min	No significant differences
KEY SUPPORTIVE STUDIES					
[redacted]	348 / 1m-6y	NR (implied 100% in both groups)	M: 45 min CH: 35 min	M: 30 min CH: 60 min	M shorter duration
[redacted]	60 / 1-8y	M: 73.3% # MZ: 36.7% #	M: 24.1 min # MZ: 18.63 #	NR	M better sedation induction P = 0.004

EEG success was measured as a composite endpoint with adequate sedation in [redacted] and time to adequate sedation was recorded instead of sleep onset latency.
CH: chloral hydrate; M: melatonin; MZ: midazolam; NR: not reported; SOL = sleep onset latency; T: Triclofos

Efficacy Evaluation in Recent Systematic Reviews

The efficacy and safety of melatonin and triclofos for inducing adequate sedation for sleep EEG were also discussed [redacted] in a systematic review and meta-analysis in children <18 years of age. The meta-analysis included data on efficacy of triclofos in 1,284 and melatonin in 1,532 children, across 16 publications. The indirect comparison between the pooled estimate of all children receiving individual medications revealed comparable efficacy in obtaining successful sleep EEG record with a single dose (overall: T=90% vs. M=76%, p=0.058, children with behavioural problems T=79% vs M=71%, p=0.25). After administration of the second dose, successful sedation could be achieved in an additional T=5% and M=6% of patients (p=0.74). The frequency of detection of epileptiform abnormalities (T=31.8%, M= 46.0%, p=0.06), and sleep onset latency (T=34.3±6.1 min, M=24.2±7.3 min, p=0.06) were not statistically significantly different although they numerically favoured melatonin. Considering safety, there were more adverse effects in children receiving triclofos (T=16.8%, M=1.27%, p=0.001). The adverse effects of melatonin were mainly vomiting and irritation, whereas predominant adverse effects with triclofos were excessive sedation and rarely respiratory depression, apnea, bradycardia, and hypotension. None of the children receiving melatonin suffered from any serious adverse effects while in the triclofos group, five children had serious adverse effects. In addition an unwanted longer duration of sleep was also higher with triclofos. Sleep duration was 68.2±19.4 min with triclofos compared to 25.4±6.2 min with melatonin (p=0.001) and the proportion of children reported as having excessive drowsiness/prolonged sleep duration was 11.5% with triclofos compared to none with melatonin (p=0.01).

Efficacy Conclusion for Sedation in Children and Adolescents

In summary, the chosen pivotal study and two supportive studies clearly demonstrate the efficacy of melatonin in allowing the successful completion of EEG (primary endpoint) when compared to suitable comparator products and these results are fully supported by the evidence from current consensus guidance / clinical guidelines from various NHS trusts which advise the use of melatonin in this indication.

Safety for Sedation in Children

There were no significant safety concerns in any studies where melatonin was used as a sedative. The most common AEs reported during use of melatonin were nausea and vomiting.

Table 15 Efficacy of Melatonin in Paediatric Sedation

Study	N	Dose/Duration/FU	Indication / Population	Findings
Pivotal Randomised Controlled Studies				
[redacted]	228 (114/group) (6m – 18y)	Melatonin Syrup (Noctura®(3mg/5 ml), Fourrts India laboratories Pvt Ltd.). Initially 0.3 mg/kg for children <10 kg, 3 mg for children of 10-15 kg and 6 mg for those weighing more than 15 kg. After 45 min with no sleep onset, a further 50% of the initial dose could be given to a maximum combined dose of 10 mg. FU – 24h	Diagnostic procedure: Sedation for EEG with sleep deprivation. (6m-18y)	Efficacy and tolerability of Melatonin vs Triclofos to achieve sleep for pediatric EEG: A single blinded randomized controlled trial The proportion of successful EEG was 89.4% in Melatonin and 91.2% in Triclofos. First dose was effective in 64% in Melatonin and 63.15% in Triclofos group. Augmentation dose was needed in 25.4% in Melatonin and 28% in Triclofos group. Mean total sleep duration was 80 min after Melatonin and 82.39 after Triclofos administration. Adverse effects were observed in 6.14% of Melatonin and 8.65% of Triclofos group. In the Melatonin group, adverse effects- were drowsiness, headache and irritability. There was no significant difference between efficacy and tolerability of Melatonin and Triclofos. Melatonin can be safely used to achieve sleep for EEG in children.
Supportive Controlled Studies				
[redacted]	348 (174/group) (1m-6y)	Melatonin 2-6 mg IR (NuPharm Laboratories Ltd, England) or chloral hydrate FU – 24h	Diagnostic procedure: Sedation for EEG-partially sleep deprived	Sleep onset latency was similar (median values melatonin 45 min, chloral hydrate 35 min, Mann-Whitney test, p=0.113). Sleep duration (median values melatonin 30 min, chloral hydrate 60 min, Mann-Whitney test, p<0.0001) and drowsiness time were significantly shorter with melatonin (median values melatonin 20 min, chloral hydrate 60 min, Mann-Whitney test, p<0.0001) which the authors considered an advantage. A second dose was required for 20 patients in the melatonin group and 6 patients in the chloral hydrate group. Few adverse drug effects were recorded in both groups.
[redacted]	60 (30/group) (1-8y)	Liquid oral melatonin 0.3 mg/kg dissolved in water or midazolam 0.75 mg/kg	Diagnostic procedure: Sedation for EEG	The prespecified primary composite endpoint of adequate sedation (Ramsay sedation score of 4) with recording of EEG was achieved in 36.7% of midazolam group and in 73.3% of melatonin group, (p = 0.004). Time from drug administration to being adequately sedated (in minutes) was 24.1 ± 9.6 for melatonin and 18.63 ± 10.51 for midazolam (P=0.1). The Ramsay sedation score of four was obtained in all children who achieved adequate sedation 40 minutes after taking the drugs. Transient agitation was seen in 6.6% of midazolam group. No significant difference was observed from the viewpoint of side effects frequency between the two drugs, (p = 0.15).
[redacted]	50 (27 epileptic) open X-O design (1-18y)	Liquid oral melatonin (dissolved) (children ⩽7 years, 5 mg; children >7 years, 10 mg) with sleep deprivation or sleep deprivation alone FU - NS	Diagnostic procedure: Sedation for sequential EEG with full sleep deprivation + EEG at 7.30am	Successful sleep onset (induction time after starting EEG recordings) occurred after a median time of 5 min in both the melatonin +sleep deprivation period (range 2–7 min) and in the sleep deprivation alone period (range 3–7 min) (p=0.544). 92 of 100 EEGs were successfully performed without significant differences between the two groups (all at 7.30 am).

Study	N	Dose/Duration/FU	Indication / Population	Findings
[redacted]	565 Sleep deprivation n=246 Melatonin n=176 Combined intervention n=143 (1-17y)	per local standard of care FU - NS	Diagnostic procedure: Sedation for EEG	Stage II sleep was achieved in 69% after sleep deprivation, 77% with melatonin, and 90% with both combined ($p<0.001$, $\chi 2$). In children who slept, there was no difference between interventions in eliciting epileptiform discharges. In children who did not sleep, epileptiform abnormalities were seen more often after melatonin or combined interventions than after sleep deprivation alone ($p=0.02$, $\chi 2$). Seizures were rare (4-6%) in all groups.
[redacted]	803 (0.5-17.7y)	chloral hydrate alone vs sequential melatonin IR # (2.5mg if <5y, 5mg if >5y), hydroxyzine (if needed), and CH (if needed).	Diagnostic procedure: Sedation for EEG	Sleep EEG recordings were obtained in 364/ 385 (94.6%) using chloral hydrate and in 409/418 (97.9%) using the sequential protocol. The percentage of children requiring CH dropped from 37.1% to 6.7% ($p < .001$). The administration of melatonin alone was successful in achieving sleep in 44.6% of the 213 children who failed to sleep spontaneously,
[redacted]	332 Analysed Melatonin 129 sleep deprivation 113 (1-16y)	Liquid oral melatonin: 1 to 4 years - 3 mg 5 to 16 years- 6 mg, 15 min prior to electrode application. FU - NS	Diagnostic procedure: Sedation for EEG	Melatonin alone and sleep deprivation alone were equally efficient in inducing sleep overall (70% in both groups). Significantly more children aged 1-4 years obtained sleep after melatonin intake in comparison to sleep deprivation (82% vs. 58%, $p\leqslant 0.01$). Melatonin did not affect occurrence of epileptiform discharges in the EEG.
[redacted]	195 Melatonin n=173 retrospective chloral hydrate n=22 (0-14y)	Liquid oral melatonin IR (Swanson®, manufactured by Swanson Health Products, USA dissolved in water) 3mg for children < 15kg, 6mg for those > 15kg 60 min before EEG. FU – 60min	Diagnostic procedure: Sedation for EEG	150 (86.7%) children achieved stage 2 sleep, of these 5 required an additional dose of melatonin (a "top-up"). All the subjects including those who did not sleep achieved successful EEG recording. The median sleep latency was 44.5 minutes, with interquartile range of 30 -67 minutes. The median duration of sleep was 25 minutes (range 18.5 – 29 minutes). None of the children had post sedation irritability or persistent drowsiness. In the retrospective chloral hydrate cohort, 21/22 (95%) achieved stage 2 sleep, while artefacts were noted in 19 (86.3%).
[redacted]	136 (68/group) (mean 8.42y)	Melatonin IR # 2.5mg (<5 years of age) or melatonin 5mg (≥ 5 years) alone or sleep deprivation alone FU - NS	Diagnostic procedure: Sedation for EEG	No difference in the number of children who went to sleep was seen. No significant difference is the macrostructure of sleep was seen, other than a reduced sleep latency for the melatonin group ($p<0.01$).
Uncontrolled Studies				
[redacted]	70 (26 – 194 months)	Liquid or capsule oral melatonin 1 to 6 years - 10 mg, > 6 years - 20 mg	Diagnostic procedure: Sedation for EEG	Sleep was obtained in 56 children (80%) with mean sleep latency of 25 ± 7.9 min (15-45) & mean sleep duration of 17.1 ± 8.6 min (5-55). 28 children (50%) woke spontaneously after 13.2 ± 7.9 min (5-40). Sleep was obtained in 13/18 children (72%) with severe behaviour problems preventing interpretable awake EEG recording.

Study	N	Dose/Duration/FU	Indication / Population	Findings
		either capsules or dissolved in water, depending on age, given just before EEG recording		
[redacted]	247 (0.5-6y)	Liquid or crushed oral melatonin 2-10 mg in baby bottle or snack 1 to 3 years - 2 to 5 mg 3 to 6 years - 5 to 10 mg A second dose was administered 30 min later if needed to a maximum dose of 10 mg.	Diagnostic procedure: Sedation for auditory brainstem responses	206 (83.4%) successfully underwent both ears testing. The delay to sleep was variable with a mean of 32 min. The quality of sleep was described as continuous in 156 infants (75.7%) and discontinuous in 50 infants (24.27%) requiring either simple nursing or a second dose of melatonin 30 min later.
[redacted]	163 (1-16y)	Oral melatonin 2-10 mg just before the EEG recording	Diagnostic procedure: Sedation for EEG	Sleep was obtained 79% after an average of 33 minutes. Yield of epileptiform abnormalities was similar to that reported in the literature for sleep-deprived EEGs. There was no significant adverse effect.

AC=active comparator, DB=double blind, DR=dose ranging, OL=open-label, PC=placebo-controlled, PG=parallel group, R=randomised, SB=single blind, XO=cross-over

Table 16 Posology and Melatonin Exposure by Age and Procedure in Studies of Paediatric Sedation

Study	neonate <28 days old		infant 1m – 2y old		child 2y – 5y old		child 6y-11y old		adolescent 12y – 17y old	
	N	Dose	N	Dose	N	Dose	N	Dose	N	Dose
DIAGNOSTIC PROCEDURES (EEG/MRI/ABR)										
Randomised Controlled Studies										
[redacted] EEG			174 (1m-6y)	2-6 mg						
[redacted] EEG			30 (1-8y)	0.5 mg/kg or 0.75 mg/kg						
[redacted] EEG			50 (27 epileptic) (1-18y)	5 mg, children ⩽7 years			10 mg, children >7 years			
[redacted] MRI			49/98 (0.3–10.3y)	3mg, Children less than 15 kg, 6 mg children heavier than 15 kg.						
[redacted] Auditory brainstem response			246 (12-48m)	0.5mg/kg						
Other controlled studies										
[redacted] EEG			Melatonin n=176/565 Combined 143/565 (1-17y)	Dose NS (per local standard of care)						
[redacted] EEG			155/418	2.5mg if <5y			263/418	5mg if >5y		
[redacted] Audiometry brainstem response			45/56 (1-6y)	5mg			11/56 (6-14.5y)	10mg		
[redacted] EEG			129 (2.8-9.8y)	Not stated						
[redacted] EEG	173 (0-14y)	3mg for children < 15kg, 6mg for those > 15kg								
[redacted] EEG	68 (Range – NS, mean 8.42y)	2.5mg (<5 years of age) or melatonin 5mg (⩾ 5 years)								

Study	neonate <28 days old		infant 1m – 2y old		child 2y – 5y old		child 6y-11y old		adolescent 12y – 17y old	
	N	Dose	N	Dose	N	Dose	N	Dose	N	Dose
Uncontrolled Studies										
[redacted] auditory brainstem response			29 (1-6y)	5 mg for children less than 6 years old, 10mg for older children						
[redacted] EEG					70 (26–194 months)	10 or 20 mg				
[redacted] auditory brainstem response			247 (0.5-6y)	2-10 mg						
[redacted] MRI			64 (10m to 5y)	Not stated in abstract						
[redacted] MRI			40 (14m to 17y8m)	10 mg						
[redacted] MRI in suspected juvenile idiopathic arthritis					15 (3-6y)	10 mg				
[redacted] MRI	110 preterm and term newborns	melatonin-tryptophan-vitamin B6. 2-3 mg								
[redacted] brainstem audiometry			250 (1 month to 13.7 years)	5-20 mg						
[redacted] EEG			163 (1-16y)	2-10 mg						
Systematic Reviews										
[redacted] brainstem audiometry			480 (1m – 14y)	0.25-20 mg						

Study	<28 days		1m – 2y		2y – 5y		6y-11y		12y – 17y	
	N	Dose	N	Dose	N	Dose	N	Dose	N	Dose
MINOR PROCEDURES (PHLEBOTOMY / VENEPUNCTURE/PARENTAL SEPARATION / MASK INTRODUCTION)										
Randomised Controlled Studies										
[redacted] Steal induction			n=47, (12-71m)	0.3 mg/kg						
[redacted] before IV sedation/dentistry					23 (2-6y)	0.5 mg/kg				
[redacted] endotracheal intubation	30 ≤32-wk gestation	IV 10 mg/kg								
[redacted] venepuncture					(25/group) (5 – 15y)	oral MT 0.5 mg/kg or 0.75 mg/kg				
[redacted] phlebotomy			30 (1-14y)	0.5 mg/kg BW, max 5 mg						
Other controlled studies - none										
Uncontrolled Studies - none										
Systematic Reviews - none										

Study	<28 days		1m – 2y		2y – 5y		6y-11y		12y – 17y	
	N	Dose	N	Dose	N	Dose	N	Dose	N	Dose
PRIOR TO OR AS AN ADJUNCT TO GENERAL ANAESTHESIA										
Randomised Controlled Studies										
[redacted] before GA for dentistry					44 (3-6y)	0.5 mg/kg,				
[redacted] before general anaesthesia							46 (5-14y)	0.5 mg/kg		
[redacted] before general anaesthesia							40 (8-14y)	0.5 mg/kg, max 20 mg		
[redacted] before N_2O/O_2 sedation					30 (3 - 8y)	3mg (G1) or 0.5 mg/kg (G2)				
[redacted] before general anaesthesia and surgery					148 (36-39/group) (2-8y)	0.05, 0.2, or 0.4 mg/kg (maximum 20 mg for all doses)				
[redacted] GA for oesophageal dilatation					100 (25/group) (3-9y)	0.1 mg/kg				
[redacted] Preoperative sedation					15/group (2-5y)	0.1, 0.25 or 0.5 mg/kg				
Other controlled studies - none										
Uncontrolled Studies - none										
Systematic Reviews										
[redacted] before general anaesthesia	358	Placebo, Melatonin or Midazolam	Premedication before general anaesthesia							
[redacted] anaesthetic indications	Not stated in abstract	Melatonin	Melatonin for anaesthetic indications							

UK Clinical Practice and NHS Guidance Documents for Sedation in children and adolescents to Facilitate EEG

Contrary to the risks associated with midazolam and chloral hydrate, melatonin presents an effective and better tolerated product with less risks associated with its administration. Melatonin has been well-established in medicinal use for paediatric sedation for EEG within the EU for more than 10 years, with recognized efficacy and an acceptable level of safety. Melatonin is firmly established in clinical practice with [redacted] and [redacted]) being followed across the NHS and incoporated into regional guidance. Numerous clinical practice guidelines and local NHS information sheets describing the use of melatonin as a sedative for EEG procedures clearly indicate that it is being widely used in the clinic and has been for a significant period of time with some guidelines / information sheets dating back to 2005, with publications reporting the clinical use of melatonin as a sedative dating back to 2001.

The [redacted] conducted an audit across fifty one NHS Clinical Neurophysiology departments in the UK in 2013 (with subsequent 'Guidelines for Paediatric Sleep EEGs' published in 2015) and concluded that melatonin combined with sleep deprivation proved to be more effective in promoting sleep in comparison with either melatonin or sleep deprivation alone. Further of the fifty-one Clinical Neurophysiology departments that took part in the Audit, forty were already using melatonin for Sedation in EEG. Further, the [redacted] state that melatonin at doses between 0.5 and 12mg are commonly used as a sedative agent in children undergoing procedures such as electroencephalography (EEG), as an alternative to sleep deprivation that does not affect the EEG morphology.

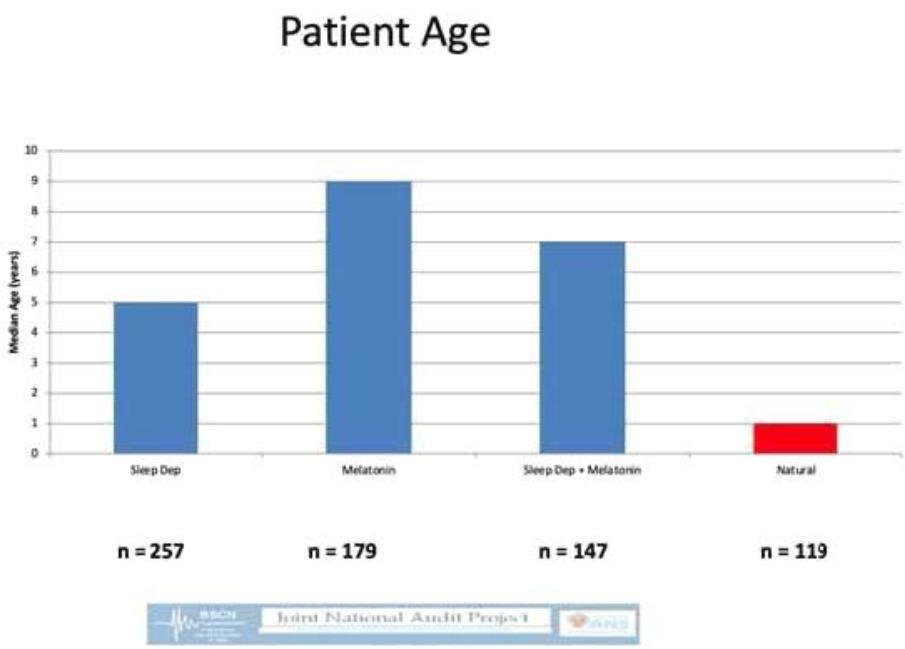
The majority of sleep EEGs requiring a sedative / hypnotic are in children rather than adolescents with most studies conducted in the <12 age group. [redacted] a slide set for the Joint ANS/BSCN audit meeting in October 2014 on melatonin, sleep and EEG. This included a detailed review of procedures and outcomes from 51 NHS Clinical Neurophysiology departments in the UK. As shown in Figure 6, the median age for obtaining natural sleep for the EEG was 1 year, with medians of 5, 9, and 7 years for sleep deprivation, melatonin, and combined sleep deprivation and melatonin respectively.

Studies regularly find melatonin to be more effective in younger children or children with developmental delay [redacted] While melatonin is occasionally used in adults, the majority of the use for EEG is in the age range included in the pivotal study [redacted] which recruited patients from 6 months to 18 years. Indeed 7 of the studies in Table 15 include patients above 12 years of age. Similarly, a recent meta-analysis [redacted] with the primary objective to compare the efficacy of oral triclofos against melatonin in achieving adequate sedation for obtaining successful sleep EEG records in children aged less than 18 years with/without any developmental delay/behavioral problems concluded that the efficacy of triclofos and melatonin are comparable. As such although use is likely to be most prevalent in children under 12, the Applicant considers it appropriate to include adolescents up to the age of 18 in the proposed posology in line with the chosen pivotal / supportive studies.

The Applicant considers that limiting the indication to children over 1 year of age significantly reduces the already negligible risk with respect to benzyl alcohol. This also takes account of the results of the national audit (Figure 6) which indicate that natural sleep is likely for children below a year old i.e. a sedative is unlikely to be needed.

The Applicant considers that the age range of 1 to 18 years is appropriate and justified by the literature, NHS use and safety and effecacy in the pivotal and supportive studies,

Figure 6: Patient Age from the UK Audit of Melatonin, Sleep & EEG



Proposed Posology

The Applicant has based the proposed dosing schedule on that used in [redacted] (pivotal study) but has simplified it further to 3mg for children less than 15kg and 6mg for children more than 15kg. While this does require knowledge of the child's weight, melatonin is normally prescribed for use in tertiary centres, and is prescribed by the child's paediatrician in the context of regular paediatric clinic visits which record height and weight at the start of each appointment. As such the proposed posology by weight does not increase the resource burden on the EEG clinic / NHS.

The rationale for the proposed posology is based on the average weight of a 1 year old child (lowest age in proposed posology) of approximately 9kg considering the 0.3mg/kg dose used in [redacted] was only for children weighing less than 10kg. Based on the good safety profile of melatonin it is considered acceptable to simplify the dosing schedule, rather than propose a dose per kg for children below 10kg and then have separate doses for children weighing 10-15kg and 15kg+ particularly when the population of children attending for an EEG aged over 1 year of age and weighing less than 10kg will be limited in number.

The proposed doses, based on the pivotal study, also fall broadly within established practice and in line with those proposed in guidelines from the [redacted] the [redacted] conducted in [redacted] and the [redacted] published in 2015. The [redacted] guidelines suggest melatonin doses between 0.5 and 12 mg being commonly used as a sedative agent in children undergoing procedures such as electroencephalography (EEG), as an alternative to sleep deprivation that does not affect the EEG morphology. Furthermore, the [redacted] which summarise current clinical practice across the UK in their guidance standards recommend up to 6mg melatonin may be given as first dose for children and infants up to 5 years and up to 12 mg may be given in older children. It should be noted that existing

guidelines will have been written in the absence of a product with a licensed indication in the UK and, as highlighted in the 2013 Audit, dosing will have at least partly been based on the availability of melatonin products (approved or imported). As such the Applicant considers that basing the proposed posology on the pivotal study in which efficacy was demonstrated for immediate release melatonin is the most appropriate approach to take.

Augmentation doses were used in pivotal, supportive and other studies when sleep onset / adequate sedation was not achieved in the pre-specified time. The Applicant is proposing an augmentation dose of 50% of the initial dose if sleep has not been initiated after 45 minutes from the initial dose, in line with the pivotal study ([redacted]), and which can be safely given without exceeding the maximum daily intake limit for benzyl alcohol.

The Applicant has included in the proposed posology that only **one** melatonin assisted EEG should be performed per 24 hour period. Whilst it is known that the greatest risk of accumulation is in neonates (due to metabolic immaturity) who are not part of the target population, two doses with augmentation doses within 24h would be over the threshold for benzyl alcohol for some children. The 24h period is considered sufficient period of time between doses as the benzyl alcohol provided by the proposed product / dose should be adequately metabolised within a short timeframe, well within the 24 hours.

As use in sedation is for a single use, short -term approach to help diagnose a condition by facilitating an EEG, the number of sedated EEGs required for any given patient will be very low. Patients who require continuous EEG monitoring are frequently either comatose, have received sedating epilepsy rescue medications such as midazolam, or are admitted for a short period of EEG with video telemetry where natural sleep is expected. Therefore it is not considered appropriate to include a warning regarding the maximum number of melatonin aided sleep EEG in a year. The proposed wording indicating melatonin is for short term, single use (once per 24 hours) to facilitate EEG is considered appropriate and clear.

Overall Conclusion for Sedation in Children and Adolescents to Facilitate EEG

It is evident from the availability of multiple guidance / patient information leaflets from numerous NHS trusts dating back to 2005, and numerous national consensus guidelines e.g. [redacted] and [redacted] that melatonin is in well-established use in the UK for sedation to aid sleep EEG.

The chosen pivotal study [redacted] and key supportive studies [redacted] demonstrate the efficacy of immediate release melatonin in the proposed indication by meeting the primary end-point of successful completion of the sleep EEG [redacted]

In 3 clinical studies across 636 children upto 18 years of age, melatonin was effective in ensuring that the sleep EEG could be completed (Melatonin 89.4% versus Triclofos 91.2%[redacted]; Melatonin 73.3% versus Midazolam 36.7%[redacted]). An augmentation dose of melatonin was needed in upto 25.4% of patients.

The proposed population and posology is taken from the pivotal study and as such is considered both appropriate and suitably justified. The requirement for augmentation doses and the frequency of melatonin use in sleep EEG has been fully discussed and the posology justified both in terms of safety and efficacy. The Applicant considers that the age range of 1 year to 18 years is appropriate and justified by the literature, NHS use, and guidance documents. Single use of melatonin for short-term sedation under medical supervision to facilitate EEG in children and adolescents from 1 to 18 years of age has been shown to be safe and effective in the pivotal and supportive studies.

4.4 Jet Lag

Critical Appraisal of Submitted Studies.

There is no regulatory Guidance document for studies in jet lag. Neither are there are any clinical consensus guidelines regarding the design of studies in jet lag, nor agreement on the most appropriate endpoints, and how these relate to clinical effect. Consequently, the pivotal studies for the assessment of the efficacy of melatonin for jet lag is based on double blind, randomised, placebo controlled trials using various primary endpoints, and systematic reviews. Supportive studies include mechanistic pharmacodynamic studies such as dim light melatonin onset (DMLO) and phase shift models undertaken in sleep laboratories

The efficacy of melatonin in the jet lag indication is supported by the evidence from these RCTs which were considered as either pivotal or supportive studies. Of the 18 publications, 16 studies were either RCTs or double-blind controlled trials (Table 17, Table 18) and 2 publications were systematic reviews. All of these 16 studies were considered of high quality with either RCT study design or prospective sample size calculation with a relevant sample size and relevant outcome measures that were measured in a standard, valid and reliable way. The studies also had no significant methodological concerns on review of the publication.

The total study population in the pivotal studies included approximately 2000 participants, with a dose of 0.3 to 10 mg melatonin either as immediate or sustained release preparations and duration of use ranging of up to 5 days. The timing of melatonin administration varied but were mostly given at bedtime or in the evening for up to 5 days post flight. The study populations were often healthy volunteers or those with experience of transcontinental flights including flight crew. Based on the dosage and duration of use in the pivotal studies, the proposed posology is aligned with data in the pivotal and supportive studies.

Overall, given the consistency in the findings from a number of pivotal studies, conducted by a range of independent investigators from 1986 through to 2013, the conclusions from the systematic reviews, the supportive pharmacodynamic and modelled studies and widespread clinical in use data, it is clear that there is an overwhelming weight of evidence to consistently support the efficacy of immediate release melatonin for jet lag in the dose ranges and posology that are being proposed.

Melatonin products as supplements, unlicensed medicines and as licensed medicines have been used for many decades in the treatment of jet lag symptoms, a fact recognised by the [redacted] / The[redacted] commented at the time that 'commercially synthesised melatonin is now being used to prevent jet lag although it is not licensed as a medicine in the UK.' Furthermore in 2009 NICE introduced a Clinical Knowledge Summary (CKS) for jet lag which included melatonin despite no licensed products being available in the UK. [redacted] .

Table 17 Design of Efficacy Studies - Melatonin in Jet lag

Stndy	N [n]/ Sex /Age	Melatonin Dose/ Formnlation/ Dnration	Design	Popnlation	Time Zones / Lag	Endpoints
PIVOTAL						
[redacted]	972 adults	0.3 mg – 10 mg IR	Systematic Review	Shift workers, individnals with jet lag	NA	Objective measures: Polysomnographic recording (PSG); Actigraph; Saliva samples; Blood samples; Electroencephalogram (EEG); Accelerometers; Honrs of sleep; Heart rate/Heart rate variability (HR/HRV); Melatonin assays; Mnltiple sleep latency test (MSLT); Urine samples; 5- min reaction test Snbjective measures: Visual Analog Scale (VAS); Sleep diaries; Stanford Sleepiness Scale (SSS); Profile of Mood States (POMS); Karolinska Sleepiness Scale (KSS)
[redacted]	339 Norwegian physicians (203 M/136 F) with a mean age of 44 ± 7a	5 mg or 0.5 mg melatonin capsules vs. placebo taken daily at bedtime on travel day and post-travel days 1-5	R-PC-DB	Norwegian physicians	Six time zones eastward	6TZE, Columbia Jet Lag Scale
[redacted]	320 volnnteers who had flights over 6-8 time zones (172 M/148 F) with a mean age of 36 ± ND	5 mg fast-release (FR), 0.5 mg FR, or 2 mg controlled-release melatonin vs. placebo taken once daily at bedtime dnring 4 days after an eastward flight	R-PC-DB	Healthy Volnnteers	6 to 8 time zones	POMS, sleep diary, symptom qnestionnaire, KSS
[redacted]	11 normal healthy male volnnteers with a mean age of 38.2 ± 9.7	3 mg snstained release melatonin capsnle vs. light treatment + 3 mg melatonin capsule vs. placebo capsule vs. light treatment. Capsules were administered at 1600h on day 2, light treatment from 0600-0800h on day 3	R-PC-DB	Healthy Volnnteers	NA	Melatonin assays, saliva samples, actigraph
[redacted]	88 normal healthy male subjects were 26–54 years in age (40.7±10.5 yr; mean ± SD)	3 mg regular release (RR), 3 mg sustained release (SR), and 3 mg snrge-sustained release (SSR; consisting of 1 mg RR and 2 mg SR) melatonin or placebo	R-PC-DB	Healthy Volunteers	NA	Circadian phase, saliva samples, saliva melatonin dim light melatonin onset (DLMO) or offset
[redacted]	20 volunteers with experience of transcontinental flights throngh at least 5 time zones (12 M/8 F) with	5 mg melatonin capsule vs. placebo taken once a day on pre-flight days 1-3 (between 1000 h and 1200 h), dnring flight, and once a day for post-flight days 1-3 (between 2200-2400 h)	R-PC-DB	Healthy volunteers with experience of transcontinental flights	5 time zones	VAS, POMS, hours of sleep, retrospective jet lag ratings

	an age range from 28-68c					
[redacted]	Healthy adults (25M, 19F) between the ages of 19 and 45 years	0.5 mg and 3.0 mg melatonin IR 3 d of a gradually advancing sleep/dark period (wake time 1 h earlier each morning), bright light on awakening [four 30-min bright-light pnlses (approximately 5000 lnx) alternating with 30 min room light < 60 lnx]	R-BS	Healthy adults	NA	dim light melatonin onset was measured before and after treatment
[redacted]	137 healthy volnnteers (70 male, 37 female, aged 18-68 years)	melatonin 5 mg, zolpidem 10 mg, a combination thereof or placebo capsnles on the eastbonnd flight back to Switzerland and once daily at bedtime on four consecutive days after the flight	DB-R-PC	Healthy adnlts	6-9 time zones	VAS to assess overall jet lag ratings and treatment effectiveness, daily sleep logs, symptoms qnestionnaires, and the POMS
[redacted]	37 regular travellers (18 M/12 F) mean age 36.3 ± 8.9 (melatonin gronp) and 35.7 ± 6.4 (placebo group)	8 mg melatonin capsule vs. placebo taken on day 1 (2200 h) and days 2-4 at bedtime	R-DB-PC	Participants accnstomed to intercontinental flights	Eastward jonrney	Global treatment efficiency VAS, sleepiness and mood VAS, sleep VAS
[redacted]	52 participants from an Air New Zealand cabin crew (26 M/25 F) with a mean age of 34.9 ± 7.7	5 mg melatonin capsule vs. placebo taken daily between 0700-0800, 2-3 days prior to retnrn flight, and between 2200-0000 h nntil 5 days after retnrn home	R-DB-PC	Air New Zealand cabin crew	12 time zones	VAS, SSS, retrospective jet lag VAS, POMS
SUPPORTIVE						
[redacted]	17 healthy volnnteers (7 M/10 F) with mean age of 48.5 ± 2.2	5 mg melatonin capsule vs. placebo taken at 1800 h on the day of their transcontinental flight departnre for the two preceding days, and between 22002400 h on the first fonr days after their return flight	DB-PC	Healthy volnnteers	8 time zones	VAS mood, VAS sleep, VAS jet lag, nrine samples
[redacted]	27 participants from a US Air Force Reserve Unit (18 M/9 F) with a mean age of 35.3 ± 8.1	5 mg melatonin pill vs. 300 mg slowrelease caffeine vs. placebo administered preflight (1700 h) and daily from day 1 (arrival day; 1600 h) -day 5 (2300 h)	R-DB-PC	Participants US Air Force Reserve Unit	7 time zones	PSG, sleep diary, MSLT, piezoelectric accelerometer, sleep VAS
[redacted]	Healthy participants aged 22 ± 4 years	5 mg IR melatonin	R-DB-PC	Healthy participants	NA	dim light (~1.9 lux, ~0.6 Watts/m2)-placebo, dim light-melatonin (5 mg), bright light (~3000 lnx, ~7 Watts/m2)-placebo, and bright light-melatonin on circadian phase.
[redacted]	Army aircrews dnring a training mission involving rapid deployment to the Middle East and night operations,	Melatonin (10 mg) or a placebo (cellulose) was administered prior to travel (stndy days 5-7), on the day of travel (stndy day 8), and for 5 d after arrival at the destination (stndy days 9-13)	R-DB-PC	Army aircrews	10 time zones	Cognitive performance

	ranging from 24-41 yr of age					
[redacted]	31 volunteers (28 males and three females), all traveling to the East Coast of Australia	5 mg/day Melatonin or placebo capsules	DB-PC	Healthy volunteers	10 time zones	Grip strength and intra-aural temperature, jet lag on a VAS scale and responses to a Jet Lag Qnestionnaire (incorporating items for tiredness, sleep, meal satisfaction and ability to concentrate)
[redacted]	NA	MEL 0.5 to 5mg doses, oral	Systematic review	NA	>5 time zones	NA
[redacted]	8 Healthy snbjects aged 20 to 32, nnderwent a 9-hr advance shift	5 mg melatonin or placebo at 1800 hr local time for 3 days before the time shift and at 1400 hr for 4 days afterwards for two periods each of 15 days' dnration	DB-CR	Healthy snbjects	NA	9h advance in sleep lab hormone +electrolyte rhythms
[redacted]	Reservists of the US Air Force aged between 19 and 47 years [mean age 35.3 (SD 8.1) years]	Synthetic melatonin was administered at 5 p.m. (US time) the day before leaving (Day -1), at 4 p.m. (US time) for the day of the flight (day 0) and at 11 p.m. (French time) for the 3 following days.	R-DB-PC	Healthy subjects	10 time zones	Saliva and urine samples

DLMO=dim light melatonin onset, EEG=electroencephalogram, FR=fast release, HR/HRV=heart rate/heart rate variability, IR=immediate-release, KKS=Karolinska sleepiness scale, MSLT=multiple sleep latency test, POMS=profile of mood states, PSG=polysomnographic recording, RR=regular release, SR=sustained release, SSR=surge-sustained release, SSS=stanford sleepiness scale, VAS=visual analog scale, TZE=time zones eastward

Summary of Pivotal and Supportive Studies for Jet Lag

Eighteen publications including randomised controlled trials (RCTs) of melatonin were identified by the literature search. These comprised 2 systematic reviews [redacted] and 5 publications reporting RCTs on phase changes induced in sleep labs simulating time zone changes [redacted].

The efficacy of melatonin in the jet lag indication is supported by the evidence from these RCTs which were considered as either pivotal or supportive studies. Of the 18 publications, 16 studies were either RCTs or double-blind controlled trials and 2 publications were systematic reviews. All of these 16 studies were considered of high quality with either RCT study design or prospective sample size calculation with a relevant sample size and relevant outcome measures that were measured in a standard, valid and reliable way. The studies also had no significant methodological concerns on review of the publication [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Subjects included in these publications were adults with ages ranging between 18 years to 80 years and included shift workers, healthy volunteers, army aircrews deployed to the Middle East and night operations, cabin crews and adult international travellers with eastward shift change. These studies included travellers with at least seven to 12 time zones with eastbound flight travel shift or phase shift induced in sleep labs simulating time zone changes.

In most of these RCT studies, the primary and secondary endpoints assessed included dim light melatonin onset (DLMO), sleep quality, daytime sleepiness, visual analog scale (VAS) rating scales of jet lag, tiredness, and drowsiness, improvements in jet lag symptoms, sleep diaries, and symptom questionnaires. Whilst there is no regulatory guidance document or clinical consensus guidelines for studies in jet lag, the primary and secondary endpoints are consistent across studies and are in line with endpoints in use for studies in other sleep disorders e.g. DSWPD.

Summary of Pivotal and Supportive Studies to Support Section 4.1 Indication

The primary endpoints of the RCTs showed improvements in jet lag symptoms following melatonin treatment in 14/16 publications (Table 18) and these were clearly stated to be statistically significant in 9 studies. Most secondary endpoints were also either numerically or statistically in favour of melatonin as described in the individual study summaries in Section 2.7.3. The effects of melatonin to resynchronise the circadian rhythm were greatest when there was alignment between the different influences (light, activity levels, food restriction, caffeine) and the timing of melatonin administration, and all 5 studies conducted in the sleep lab showed positive effects of melatonin. Both meta-analyses reported a benefit from melatonin in the treatment of jet lag.

Table 18 Change from baseline in Primary Endpoints of Studies

Study	N	Dose/Duration	Jet Lag Paradigm	Response	Treatment difference
Pivotal Studies					
[redacted]	Eight RCTs with 972 total participants -> weak recommendation in favour of melatonin use in jet lag				
[redacted]	64	M 5mg x 5d	6TZE, Columbia Jet Lag Scale	No significant differences between groups	
	70	M 0.5mg x 5d			
	63	M 0.5mg x 5d (early evening)			
	60	P x5d			
[redacted]	~55	M0.5mg x4d	6-8TZ, varied endpoints	Sleep quality was improved by melatonin, with significantly improved latency, duration, and time awake with the 5mg dose.	
	~55	M 5mg x 4d			
	~55	MSR 2mg x4d			
	~55	Px4d			
[redacted]	11	M 3mg x1	Phase advance in sleep lab, salivary dim light melatonin onset	0.72 h**	M + morning light has additive effects
	11	P x 1		NR	
	11	Light x1		0.31 h NS	
	11	M+L x1		1.04 h ***	
[redacted]	13	M RR 3mg x1	Phase advance in sleep lab, salivary dim light melatonin onset	1.23 h **	NR
	13	M SR 3mg x1		1.44 h ***	
	13	M SSR 3mg x1		1.16 h *	
	13	P x 1		0.73 h	
	9	M RR 3mg x1	Phase delay in sleep lab, salivary dim light melatonin onset	1.12 *	
	9	M SR 3mg x1		NC	
	9	M SSR 3mg x1		NC	
	9	P x 1		NR	
[redacted]	16	M 0.5mg x3d	Phase advance in sleep lab + advancing light, salivary dim light melatonin onset	2.5 h	"significant"
	13	M 3.0mg x3d		2.6 h	
	15	P x3d		1.7 h,	
[redacted]	15	M (early) 5mg x8d	Series of internatioual flights in aircrew, jet lag VAS	64.7	-27.0**
Supporting Studies					
[redacted]	14	M (late) 5mg x5d	8TZE, VAS responder analysis (<50 on VAS)	66.7	"less severe" **
	15	P x 7d		37.7	
[redacted]	9	M 5mgx7d	7TZE, polysomnography and daytime sleepiness	Positive effects	fell asleep earlier slept longer *
	9	P x 7d			
[redacted]	9	DL-M 5mg x1	Phase advance in sleep lab, salivary DLMO	+11 min	M v P, F1,32 = 10.58,**
	9	DL-Px1		-26 min	
	9	BL-M 5m x1		+42 min	
	9	BL-P x1		+16 min	
[redacted]	15	M 8mgx4d	USA->France (TZE), treatment efficiency VAS	73	25mm*
	15	P x 4d		48	
[redacted]	~13	M 10mgx6d	USA->Middle East (8TZE) sleep cycles & vigilance	advanced 2-3h	improved vigilance * prolonged sleep *
	~13	P x 6d		shortened	
[redacted]	14	M 5mg x6d	10TZE, jet lag VAS	improved	NR, NS
	17	P x 6d		improved	
[redacted]	10	M 5mg x7d	Auckland to London to Auckland, jet lag VAS	2.15	-1.25**
	10	P x 7d		3.40	
[redacted]	9	M 5mg x NR	7TZE, salivary waking melatonin	maintained	melatonin resynchronizes hormone rhythms
	9	P x NR		shifted	
[redacted]	8	M NR	+9h in sleep lab hormone +electrolyte rhythms	NR	"enhanced"
	8	P NR		NR	
[redacted]	23	M 5mg x 5d	6-9TZE, VAS jet lag severity	decreased	NR
	23	P x5d		NR	
[redacted]	9/10 RCTs found decreased jet lag for >5TZ at 0.5 - 5mg doses, with 5mg better than 0.5mg and doses > 5mg no more effective. 2mg SR was relativly ineffective suggesting that a short-lived higher peak concentration of melatonin works better. Based on the review, the number needed to treat (NNT) is 2.				

* P<0.05, **P<0.01, ***P<0.001; BL= bright light, DL=dim light, DLMO = dim light melatonin onset, M=melatonin, NA = not applicable, NC =not calculated, NR = not reported, NS = not significant, P=placebo, RCT=randomised control trial, RR = regular release, SR = sustained release, SSR= surge-sustained release (SSR; consisting of 1 mg RR and 2 mg SR), TZE=time zones east, TZW=time zones west, VAS=visual analogue scale.

Almost all studies which included healthy volunteers with flight experience showed improvements in jet lag symptoms for the international travellers. The other symptoms such as sleep quality, fatigue and sleep latency were also significantly improved with melatonin across the different dose regimens used.

[redacted], conducted the first double-blind, placebo-controlled trial of melatonin in jet lag. The phase-shifting ability of melatonin was evaluated in 17 patients taking an eight-hour eastbound transmeridian flight. Travellers who were randomly assigned to the melatonin group (n = 8) were instructed to take 5 mg/day starting three days before the scheduled flight in the early evening (at 6 p.m.) and for four days post-flight at the bedtime hour of the new local time zone (from 10 p.m. to midnight). Subjects receiving melatonin experienced significantly fewer severe symptoms (P = 0.009) based on subjective measures, including jet lag ratings, self-recorded sleep parameters, and mood ratings. Melatonin participants also adjusted more rapidly in objective measures, such as assessments of endogenous melatonin levels and cortisol rhythms.

Norwegian physicians who had visited New York for 5 days were compared to healthy volunteers in other studies in a randomised double blind controlled study (n = 267) involving four treatment groups (placebo and three alternative regimens of melatonin (5.0 mg at bedtime, 0.5 mg at bedtime, and 0.5 mg) taken on a shifting schedule). They found a marked increase in total jet lag score in all four treatment groups followed by progressive improvement over the next 5 days [redacted]

The impact of various dosage forms of melatonin and placebo on jet lag symptoms were assessed in 320 volunteers who had flights over 6 to 8 time zones [redacted]. Subjects received either melatonin 0.5 mg fast-release formulation, melatonin 5 mg fast-release formulation, 2 mg melatonin (a controlled-release formulation), or placebo. The study medication was taken once daily at bedtime during 4 days after an eastward flight. The sleep quality was improved by melatonin in the second and third postflight night, when jet lag is usually most severe. On the second night postflight, the melatonin 5 mg group showed significantly improved overall self-rated sleep quality, and the sleep latency was significantly shorter than in all other groups. Subjects treated with melatonin 5 mg spent less time awake during the night, and it was easier for them to fall asleep and to get-up in the morning. The lower 0.5 mg melatonin dose was also seen to be as effective as the 5 mg dose but the hypnotic effects such as sleep latency were significantly greater than 0.5 mg. Therefore it concluded that 5 mg fast -release formulations were the most effective form to reduce fatigue and sleep disorders after jet lag.

Five publications reported RCTs on phase changes induced in sleep laboratories simulating time zone changes. All studies were randomised and double blind. All studies concluded that the phase advance from the combination of afternoon melatonin with next morning light is additive. In these studies, healthy adults with ages ranging between 20 to 54 years were included. These studies investigated effects of melatonin with or without the combination of light (bright or dim) conditions and showed that a combination of morning bright light an d afternoon melatonin, both timed to phase advance, can produce a larger phase advance shift than bright light alone [redacted]

In a study by [redacted] in healthy subjects with a 9-hr advance shift, no differences were found either in sleep log data (i.e., the sleep quantity and quality were rated to be similar with and without melatonin treatment) or in subjective ratings, except alertness (100-mm scale). During the day after the shift (after only 3 hr of sleep and during a shortened wake period), subjects felt significantly more alert ($p \leq 0.05$) when ingesting melatonin (5 mg) than when ingesting placebo, although no significant change was detected in subjective sleep

parameters. The difference in alertness was caused by decreased values in the placebo group when compared to baseline, whereas only a slight change was observed in the melatonin-treated group.

Dim light melatonin onset (DLMO)

Four studies assessed DLMO in phase advance in sleep lab [redacted] following treatment of melatonin under constant routine conditions. The DLMO is found by sampling melatonin concentration in the blood or saliva at uniform intervals under dim light conditions (<10 lx). An average DLMO threshold level of 10.4 pg/mL was observed with a mean phase delay of approximately 26 min in a study by [redacted]. In a study by [redacted] the mean phase shifts for each condition, calculated as the difference between DLMO from night 1 to night 3, were: a 0.72±0.11 h (mean±SEM) advance for "melatonin at 1600 hours" condition; a −0.12±0.19 h delay for the "placebo" condition; a 0.31±0.20 h advance for the "light treatment from 0700 to 0800 hours" condition; and a 1.04±0.17 h advance for the "melatonin at 1600 hours plus next morning light treatment from 0600 to 0700 hours" condition. In another study by [redacted] it was concluded that there was no difference in phase shifting efficacy between the slow and fast release preparations of melatonin. [redacted] in their study concluded that there were significantly larger phase advances with 0.5 mg (2.5 h, n = 16) and 3.0 mg melatonin (2.6 h, n = 13), compared with placebo (1.7 h, n = 15), but there was no difference between the two melatonin doses. Afternoon melatonin, morning intermittent bright light, and a gradually advancing sleep schedule advanced circadian rhythms almost 1 h/d and thus produced very little circadian misalignment. This treatment could be used in any situation in which people need to phase advance their circadian clock, such as before eastward jet travel or for delayed sleep phase syndrome.

Alertness

Effect of melatonin on morning alertness was assessed in four studies which included healthy volunteers travelling from London to the East Coast of Australia [redacted] or with advance shift [redacted] air crew members involving rapid deployment to the Middle East and night operations [redacted] and cabin crew [redacted] The analysis of activity data in air crew members suggested that melatonin may have stabilized the sleep/wake cycle by facilitating the advance of bed times (3.07 h) and rise times (2.65 h) while preventing sleep loss. Whereas, in cabin crew members who took 5 mg melatonin for 5 days after the use of placebo for 3 days, the morning alertness was improved and faster compared to the crew members who took 5 mg melatonin 3 days prior to arrival until 5 days after return home. However, in a study in volunteers travelling from London to the East Coast of Australia, melatonin had no benefit in alleviating jet lag or the components of jet lag, and it did not influence the process of phase adjustment [redacted] In another study in healthy subjects with a 9-hr advance shift in an isolation facility, only a slight change in the alertness with 100mm linear scales in melatonin-treated subjects [redacted].

Systematic Reviews

In the systematic review by [redacted] eight RCTs with 972 total participants characterized melatonin use for counteracting jet lag. Almost all of the studies were of high (+) quality, with the exception of one poor (−) quality study, which favoured neither melatonin nor control, despite a large sample size (n=339). Of the seven high (+) quality studies, one favoured neither melatonin nor control. The remaining six RCTs favoured melatonin, including two large studies (n = 320 and n = 160) and one which noted a limitation that melatonin increased tiredness the next morning.

These studies also included healthy shift workers and the use of melatonin showed to prevent phase shifts from jet lag and improvements in insomnia, but to a limited extent.

Another systematic review discussed the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet-lag after air travel across several time zones. Nine of total ten studies were chosen with adequate quality to contribute to the assessment in this review. Eight of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time [redacted].

Conclusions on Efficacy in Jet Lag

All of the above studies describing melatonin use in jet lag are considered high quality and indicate a high degree of scientific interest. To summarise, the primary endpoints of the randomised studies showed improvements in jet lag symptoms following melatonin treatment in 14/16 publications and were clearly statistically significant in 9 studies. Most secondary endpoints were also either numerically or statistically in favour of melatonin. The effects of melatonin to resynchronise the circadian rhythm were greatest when there was alignment between the different influences (light, activity levels, food restriction, caffeine) and the timing of melatonin administration, and all 5 studies conducted in the sleep lab showed positive effects of melatonin. Both meta-analyses reported a benefit from melatonin in the treatment of jet lag. In conclusion, the efficacy can be considered as demonstrated for the jet lag indication proposed for this application.

Safety of Melatonin in Jet Lag

Adverse events reported in the studies were consistent with the known safety profile of melatonin and did not raise any new safety concerns. The studies reported adverse effects of jet lag such as problems sleeping, fatigue, insomnia, decreased appetite, disequilibrium, a change in bowel habits, and headache. Further details are provided in Module 2.7.4.

Summary of Pivotal and Supportive Studies to Support Section 4.2 Posology

It is considered that Ceyesto 1 mg/ml oral solution will have a similar pharmacokinetic profile compared to other immediate release (IR) forms of melatonin. Therefore, the literature and review using other IR forms of melatonin are also considered relevant and supportive of this application. Across the pivotal and supportive studies, a melatonin dose range of between 0.5 and 10 mg was assessed. Of the 10 key jet lag studies mentioned in the meta-analysis review [redacted] 7 investigated a dose of 5 mg once daily. The review stated that for many people, 5 mg may be a higher dose than necessary, and 2 or 3 mg may therefore be preferable to start with, but a dose of 6 mg may be required if the standard dose does not adequately alleviate symptoms.

The review states that 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" and that "taking melatonin before the day of travel does not hasten or improve adaptation to local time at

destination and is not recommended.". It is therefore considered appropriate to advise that melatonin treatment should be initiated on arrival at destination with the first dose taken at the habitual bedtime. This dosage and timing of dose is also consistent with the posology for multiple approved melatonin products (tablets, capsules and oral solutions) in Europe and UK including the 3mg melatonin tablet approved in Hungary in 2003.

The review also provides evidence for duration of treatment. The jet lag studies included in the review provide limited evidence for efficacy over 4 days. However, one study, which involved travel over the greatest number of time zones (12) in both easterly and westerly directions, found overall jet lag scores to be elevated for 5 days after arrival with evidence of benefit for this period in the melatonin group. If jet lag symptoms are persisting this long, a treatment period of up to 5 days can therefore be supported provided melatonin is only taken to alleviate symptoms for the shortest period. This is consistent with the wording in the Applicant's proposed section 4.2. The pharmacodynamic effects of melatonin are dependent upon its timing with respect to the endogenous circadian rhythm and the other influences on the circadian clock, such as light exposure, food intake and activity levels. The best results in resetting the circadian clock are achieved when all influences are aligned. Therefore, patients should take melatonin within the relevant time window around a desired bedtime that is aligned with the clock time at the destination, and should support this by appropriate management of light exposure, food intake and activity levels.

To summarise, there is sufficient evidence to support the proposed dosage of 3 mg, increasing to 6 mg if needed. Although the data to support the duration of treatment of up to 5 days is not extensive, if jet lag symptoms are persisting it can be considered appropriate for use for this long provided melatonin is taken for the shortest period only.

In addition, the Applicant's proposed posology including recommended dose (3 mg), time of administration and duration of treatment (maximum of 5 days but shortest possible time) is consistent with many other approved melatonin products in Europe and the UK. This provides added support to the Applicant's proposed section 4.2 especially as it is considered important for patients and healthcare professionals to receive (as much as possible) a consistent message in terms of posology for similar products approved for the same / similar indication.

Overall Conclusions in Jet Lag

Based on a critical appraisal of the literature (including 10 pivotal studies and 8 supportive publications), melatonin can be considered as safe and effective in the treatment of jet lag in adults.

Typical symptoms of jet-lag are sleep disturbances and daytime tiredness and fatigue, though mild cognitive impairment, irritability, and gastrointestinal disturbances may also occur. Jet-lag is worse the more time-zones crossed and is typically worse following eastward travel as people generally find it harder to advance their circadian rhythm (body clock) than to delay it, as required following westward travel. Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet-lag by ~ 44%, and to shorten the duration of jet-lag [redacted]). In 2 studies of flights over 12 time zones melatonin effectively reduce the duration of jet-lag by ~ 33% [redacted] Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation of circadian rhythmicity / jet-lag, melatonin should not be taken before 20:00 hr or after 04:00 hr at destination.

The Applicant proposes a recommended dose of 3 mg which can be increased to 6 mg if needed and has presented 4 references to support this claim, most notably the review

publication [redacted] which also provides recommendations on the duration of treatment. The proposed indication and posology are also consistent with other approved melatonin immediate release products approved in Europe and the UK which provide further support and a consistency of message to both healthcare provider and patient.

Based on the totality of available clinical efficacy data, the Applicant considers that Ceyesto 1 mg/ml oral solution is appropriate for us in the short term treatment of jet lag in adults at the proposed dosage and therefore that the risk/benefit ratio is positive.

4.5 Justification of use in patients with enteral feeding tubes

The Applicant has proposed that 'If necessary, Ceyesto 1mg/ml Oral Solution can be administered via a silicone gastric, duodenal or nasal feeding tube.'

In support of this recommendation the Applicant has considered both the clinical literature and established clinical practice as evidenced by guidelines in the UK and also published reference sources used by clinicians described in Module 2.7.3. It is evident that the practice of using melatonin via enteral feeding tubes is commonplace in the UK and has been for over a decade. There are numerous NHS guidelines in place, which remain active and in accordance with current practice. It would appear that the use of melatonin via either nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tube is an established practice and for immediate use would suggest that there is no known or suspected interaction with different types of tubing used by NHS organisations. Furthermore the '[redacted] which is the primary reference source for clinicians administering via enteral routes recommends the use of unlicensed oral melatonin solution and advises against the crushing of modified release tablets in situations requiring enteral administration.[redacted].

In addition to the NHS guidance referenced above, clinical studies such as [redacted] have administered melatonin through a feeding tube as necessary by opening capsules and suspending the contents in an appropriate vehicle. [redacted] reported no degradation of melatonin (mean melatonin recovery was between 89% and 111%) when melatonin was mixed in water, orange juice, semi-skimmed milk, strawberry yoghurt, and strawberry jam, with compatibility and stability for up to 6 hours. The results appear to confirm that these specific common foods and liquids used to mix and administer the melatonin in the [redacted] trial should not compromise the integrity of the drug and should, therefore, ensure delivery of the prescribed dose.

Furthermore and as part of the development of the product, a compatibility study was performed using tubes [redacted]

[redacted]

[redacted]

Based on the results of the study the Applicant concludes that the proposed product can be used with silicone tubes but that use with polyurethane tubes cannot be recommended.

[redacted]

Overall Summary on Feeding Tubes

It is evident that administration via an NG or other type of enteral tube is a precedent that is well accepted in the UK. The Applicant considers that on the balance of evidence that has been provided including a compatibility study with the proposed product that the inclusion of advice that the product can be administered via silicone tubing in the Applicant's SmPC for an oral solution product is justified, improving patient safety, accuracy of dosing and removing the need for off-label or unlicensed practice.

4.6 Efficacy Summary and Conclusions

Melatonin has been studied extensively in DSWPD, insomnia, other sleep disorders, and jet lag, for the promotion of normal sleep that is aligned with the environmental time. It has shown substantive evidence of efficacy in normalising the circadian rhythm and promoting sleep onset with additional benefits on multiple domains of sleep and patient well-being. This is seen in patients with insomnia or other sleep disorders characterised by delay or difficulty in initiating sleep, and in patients with subjective feelings of jet lag where their internal clock is misaligned with environmental time. As the purpose of melatonin administration is to promote natural sleep that aids in aligning biological and environmental time, the timing of melatonin administration is important to its effect. Melatonin also has a well-established use in single doses for short-term sedation under medical supervision to facilitate medical procedures as documented in the literature. In all indications, it is important that patients treated with melatonin avoid circadian triggers (light, activity, food or caffeine intake) that are misaligned with the desired sleep schedule.

For treatment of sleep disorders, doses of 0.5 mg have been shown to be effective, although a better response is achieved in many subjects with higher doses up to 6mg. Doses have been optimised for each indication based on the overall risk benefit for the population and indication. The dose that adequately alleviates symptoms should be taken for the shortest period.

The use of melatonin for sedation in children to faciliate EEG recordings is a standard cliical practice, as evident from multiple national consensus guidelines, local or regional guidance documents and patient information leaflets dating back to 2005. The chosen pivotal study

[redacted] and key supportive studies [redacted] demonstrate the efficacy of immediate release melatonin in the proposed indication by meeting the primary end-point of successful completion of the sleep EEG [redacted]

5. OVERVIEW OF SAFETY

Melatonin has been administered to humans in numerous studies employing a wide range of doses and durations with double-blind placebo controlled studies of immediate release melatonin of up to 12 weeks [redacted] and follow-up periods of up to 14 months [redacted] As mentioned above, the total number of studies available in the literature include more than 10,000 patient records with the vast majority of adverse events being considered mild. In addition, data from published studies also supports the tolerability and safety of various formulations of melatonin treatment for periods up to 6 years. Clinical studies in other indications and populations have also demonstrated the good safety profile of melatonin with doses up to 240 mg, which is far in excess of the doses proposed.

Melatonin has also been marketed at doses ranging from 0.5 to 80 mg as an oral food supplement in many regions for many years without significant safety concerns, including in the United States where it falls under the FDA's Dietary Supplement Health and Education Act (DSHEA) category of "other dietary substance". The in depth evaluation of the literature data on the safety of melatonin in the US became available in April 2004 when the Committee on the Framework for Evaluating the Safety of Dietary Supplements of the National Academies announced the publication of a report entitled "Dietary Supplements: A Framework for Evaluating Safety". The report contains numerous references to melatonin and includes an 84-page prototype melatonin monograph. Conclusions and recommendations about the safety of the ingredient based on the strength of the scientific evidence were that short-term use of melatonin in a daily amount of 10 mg or less does not raise concern of harm for healthy adults who are not taking concurrent medications or other dietary supplements [redacted]

To evaluate the safety of melatonin, literature searches to identify systematic literature reviews and publications reporting adverse events (AEs) and/or the safety profile in humans conducted as randomised placebo-controlled trials (RCTs) were identified and the search strategies are provided in Appendix 2.7.4.7. The individual studies are summarised in Section 2.7.4.1.1 and a summary of the AEs reported is provided in Section 2.7.4.2. The total number of studies available in the literature included more than 10,000 patient records. All studies evaluated for clinincal pharmacology or efficacy were also reviewed for safety and theese are also summarised in Module 2.7.4.

A recent systematic literature review, [redacted] was identified as assessing the evidence for AEs associated with melatonin treatment for sleep disorders in 37 RCTs. [redacted] was used as a key meta-analysis to establish the AEs related to melatonin administration and was supplemented with additional information from later studies. An additional 4 key studies [redacted] were identified, and the safety results of these studies have also been included in the safety profile discussed below. The total number of subjects across all studies reported by [redacted] who received at least one dose of melatonin, with a dose ranging from 0.15 mg/day to 12 mg/day and a duration ranging from 1 to 29 weeks, (with the majority lasting 4 weeks or less) was 1625. The total number of subjects from the supplementary studies was 377. The evaluation of the safety profile in this overview section reflects the reporting of safety on melatonin administration in more than 2000 subjects.

A supplementary literature search was performed in the paediatric population identifying more than 70 publications in >3500 children relevant to insomnia, 33 publications reporting use of melatonin in >3000 children (birth to 18y) for paediatric sedation, prescription and other registries were reported by 6 publications in >7000 patients, neonatal indications were reported in 17 publications in >300 newborns and other paediatric indications were reported by a further 30 publications. In the paediatric population there were 4 large scale RCTs [redacted] that each included ≥100 participants. A low frequency of general mild adverse reactions has been reported in the paediatric population. The number of adverse reactions has not differed significantly between children who have received placebo compared to melatonin. The most common adverse reactions were headache, hyperactivity, dizziness, and abdominal pain. No serious adverse reactions have been observed when high quality synthetic melatonin was given together with the currently recommended posology.

Generally across populations, a consistent theme is observed with the same / similar adverse events of a mild nature generally being reported. As such immediate release melatonin is considered a safe treatment in the proposed indications and populations especially compared to other sleep medicinal products like benzodiazepine or zolpidem.

Overall, no AEs that were life threatening or of major clinical significance were identified and few, generally mild to moderate, AEs were associated with the administration of daily melatonin in all publications reviewed.

5.1 General Safety Profile

The most frequently reported AEs were those associated with the mechanism of action of melatonin such as daytime sleepiness, headache, other sleep-related Aes or dizziness. Very few AEs considered to be serious or of clinical significance were reported. These included agitation, fatigue, mood swings, nightmares, skin irritation and palpitations. Most AEs either resolved spontaneously within a few days with no adjustment in melatonin, or immediately upon withdrawal of treatment. Melatonin was generally regarded as safe and well tolerated.

Adverse Effects

Safety was reviewed in all publications submitted in this application and compared with the established safety profile of melatonin and a systematic review of the AEs associated with melatonin treatment for sleep disorders as described in Module 2.7.4. AEs were generally infrequent, mild or moderate in severity and were either self-limiting or resolved quickly on withdrawal of treatment. The frequency of AEs across studies was low, with the majority considered to be mild in severity and not significantly more frequent than for placebo. The majority of these were said to have resolved within a few days without an adjustment in dose, or immediately on withdrawal if melatonin was discontinued. Sixteen studies reported no AEs in any patients. The most common AEs by proportion of affected patients were daytime sleepiness, headache, other sleep-related AEs, dizziness and hypothermia. AE were not obviously correlated with either dose or formulation (immediate/fast-release or controlled/prolonged-release). None of the included studies reported any statistically significant difference in the frequencies of AEs between melatonin and placebo groups. It should be pointed out, however, that in the majority no statistical analysis of AEs was performed and only the numerical frequencies of symptoms were given [redacted]. The 4 supplementary studies published after [redacted], showed a similar profile of reported AEs such as daytime sleepiness, headaches and dizziness.

Few AEs were considered related to melatonin.

The AEs with the highest frequencies are listed in Table 19 below from the 37 RCTs reviewed by [redacted] and the 4 supplementary studies identified thereafter. All 5 publications studied only made specific assessment of relationship of AEs to melatonin.

[redacted] reported that overall, the rate of AEs was not markedly different from that for placebo, and very few AEs were identified uniquely in melatonin-treated patients.

Table 19 Number of studies reporting each AE with frequencies for melatonin and placebo group in all studies.

	[redacted]			Supplementary studies 2019-20		
Adverse Event	No. Studies	Melatonin subjects with AE (AE_{MLT})	Placebo subjects with AE (AE_{PLB})	No. additional studies	Melatonin subjects with AE (AE_{MLT})	Placebo subjects with AE (AE_{PLB})
Daytime sleepiness [a]	9	50	23	1	4	5
Headache [b]	15	44	32	3	12	10
Other sleep-related AEs [c]	6	21	9			
Dizziness [d]	4	14	2	1	14	5
Hypothermia [e]	2	14	4			
Decreased appetite	3	7	1			
Restlessness/Agitation	2	6	0	1	11	7
Rash [f]	4	15	9	2	7	13
Burping	1	5	0			
Tearfulness	1	5	0			
Fatigue [g]	3	25	21	3	27	22
Seizures (not increased rate)	2	12	8			
Insomnia [h]	4	7	4	1	11	10
Gastrointestinal illness/diarrhoea [i]	3	10	7	3	19	12
Muzziness/fuzzy feeling/hung-over	3	3	0			
Hyperactivity	2	4	1			
Enuresis	1	3	0			

AE adverse event

[a] Some of the studies specified 'daytime sleepiness' and others simply stated 'sleepiness' (or similar) but since it is unlikely that nighttime sleepiness after the melatonin dose would have been listed as an AE, these have been categorised together as 'daytime sleepiness'

[b] Adverse Events: $12_{MLT}, 9_{PLB}$ Adverse Reactions: 0_{MLT} 1_{PLB}

[c] Including 'red eyes', 'vivid dreams' and nightmares

[d] Adverse Events: $12_{MLT}, 5_{PLB}$ Adverse Reactions: 2_{MLT} 0_{PLB}

[e] Including 'cold feelings'

[f] Including skin irritation, pruritus and itching

[g] Adverse Events: $25_{MLT}, 22_{PLB}$ Adverse Reactions: 2_{MLT} 0_{PLB}

[h] Including 'poor sleep' and 'sleep disturbance'.
Adverse Events: $11_{MLT}, 9_{PLB}$ Adverse Reactions: 0_{MLT} 1_{PLB}

[i] Including diverticulitis, nausea and vomiting.

Adverse Events: 14_{MLT}, 12_{PLB} Adverse Reactions: 5_{MLT} 0_{PLB}

In published clinical studies, melatonin was well tolerated, and no serious side effects were associated with melatonin administration.

Review of AE in the literature

The AE terms and incidences reported across all submitted publications have been calculated for each proposed indication (Table 20) and was used to review section 4.8 of the proposed SmPC. In summary, the AEs reported are considered background rates and consistent with the reported AEs of currently approved and licensed melatonin products in the EU.

Event Terms and Classes Reported

The AEs listed in the proposed SmPC section 4.8 is compiled based on all AE from clinical trials reported in all publications for all formulations of melatonin. All overlapping or similar preferred terms (PT) have been considered together in the AE table below. Groups of other similar adverse events were consolidated under the PT.

Some AE reported which are clearly seen across the indications are those commonly associated with the melatonin safety profile, such as headaches, nausea, diarrhoea and somnolence. The slightly higher incidence of these events compared to the current labelling for melatonin is within the expected range of variation and, as most studies reported similar rates of events in the active and placebo groups, they therefore are considered to represent the background rate for the population. In longer term treatment of up to several months no additional long term adverse effects were seen. However, a small frequency of abnormal dreams occurred mainly after longer term treatment.

Cardiac disorders have been reported at an incidence between 0.63% to 0.83% has been reported, in studies across adult chronic insomnia with and without comorbidities. These studies had a larger proportion of subjects of over 55 years old where cardiac disorders are an expected event, and the rate of events was consistent with a background event related to the patient group. Similarly, a higher incidence of events which are considered characteristic of the older population can be seen for GI-disorders (13.18 – 13.66%), musculoskeletal & connective tissue disorders (10.36 – 10.74) and nervous system disorders (5.53 – 5.73%).

The higher incidences of gastrointestinal disorders, infections and musculoskeletal disorders were driven by the data from [redacted] that reported this high incidence of AE in its 26-week melatonin prolonged release treatment arm. However, the publication also reported that most AE were mild in severity with no clinically relevant differences between melatonin and placebo for any safety outcome. Likely therefore these represent a background rate of events.

The incidence for respiratory, thoracic and mediastinal disorders was higher in studies in chronic insomnia in adults with and without comorbidities. These were mainly attributed to 2 studies [redacted] Again, [redacted] reported most AE were mild in severity with no clinically relevant differences between melatonin and placebo for any safety outcome. [redacted] reported that when AEs were normalized per exposure time, the AE occurrences per 100 patient-weeks was much lower for melatonin (3.66) than for placebo (8.53). As these studies reported at a rate that was similar to (or less than) placebo and that these studies also had a higher proportion of subjects in the older population the incidence for these events can also be considered a background rate.

Infections are a common event in all populations, increased during the winter months and are particularly common in the elderly and therefore the high incidence rate seen at 12.32 – 12.77% in some studies are not unexpected.

There is an increase in the incidence frequency for raised blood glucose (0.05 – 0.06%) which the Applicant has carefully reviewed due to the potential associated risk. However, from the safety evaluated from all the publications submitted for studies in each respective indication only one study in chronic insomnia in adults with comorbidities [redacted] reported 2 out of 39 melatonin treated subjects and 1 out of 34 placebo subjects had an increase in blood glucose. However, the event was reported at a rate that was similar to placebo, and no clinical sequelae were noted. Therefore, the Applicant has not proposed any changes to the established wording around blood glucose in the SmPC.

The incidence for high alkaline phosphate (0.54 – 0.85%) has been taken into consideration. On review of this event, a patient in one study [redacted] had a significantly high level of high alkaline phosphate following melatonin treatment however there were no clinical sequelae. The relevance of this isolated event is unclear and therefore the Applicant is not recommending its addition to the SmPC.

In addition to the review of the safety data included in this application, for some event terms the Applicant has a lso referred to current class labelling and Agency advice to determine the content of the proposed SmPC.

Hypothermia

A degree of relative hypothermia, consistent with normal circadian changes, is a well recognised effect of melatonin. Melatonin at 0.5 mg, 3 mg, or 9 mg induced hypothermia in a dose-dependent manner in 6 healthy young male volunteers compared to placebo taken on a crossover basis [redacted]. A significantly suppressed core body temperature was seen at the 3-mg and 9-mg doses and slightly suppressed core body temperature at the 0.5-mg dose. There was significant positive correlation between the magnitude of core body temperature suppression and the area under the MLT concentration curve as well as the peak MLT concentration. Significant reductions in body temperature were also reported in a study of 6 younger and 10 older women following 5 mg oral melatonin [redacted] and a further 6 healthy male volunteers receiving oral melatonin 3 mg or 9 mg or placebo in a randomized, single-blind, cross-over study [redacted]

Changes in endogenous melatonin can also lead to clinically overt hypothermia [redacted]. A 6-year-old girl presented on several occasions during a 1-year period with complaints of altered consciousness, syncope, hypothermia and episodes of sweating. The episodes occurred daily and during sleep and lasted for 1-6 h. She was shown to have hypermelatoninemia (>1,000 pg/ml, normal range 0-150 pg/ml) during these episodes.

Within the clinical literature for melatonin in sleep disorders, several reports of hypothermia were identified.

In a systematic review of safety that included 37 RCTs [redacted] hypothermia was reported in 2 studies, ocurring in 14 subjects receiving melatonin and 4 subjects receiving placebo. The meta-analysis estimaetd the AE frequency corrected for placebo as 0.62%.

A case-study reported the development of hypothermia in a child with autism after a single 3 mg dose of melatonin for a nighttime sleep disorder [redacted] Body temperature decreased to 34°C half an hour after administration and remained below normal for two days.

Mild hypothermia at an incidence of 0.69 – 0.84% was reported in six paediatric patients taking melatonin in the 13-week [redacted] study [redacted]

In the study in the elderly by [redacted], a significant reduction in body temperature was seen after the administration of 3mg of melatonin.

AEs have not been reported elsewhere in the pivotal and supportive studies across all indications for melatonin and hypothermia was reported in similar numbers in the active and placebo group in another study[redacted]

The mechanistic basis for a causal link with melatonin appears likely as there is nonclinical evidence of such an effect. Hypothermia following melatonin administration is generally considered a direct qualitative effect of melatonin and has been demonstrated in rats [redacted] mice [redacted] dual-phasing rodent *Octodon degus* [redacted] and other animals. Indeed, hypothermic effects of hops are antagonized with the competitive melatonin receptor antagonist luzindole in mice [redacted]). However, increased melatonin levels may be associated with thermogenesis after torpor in hamsters [redacted] and the melatonin-related receptor GPR50 is implicated in adaptive thermogenesis and torpor [redacted].

In most cases, any changes in temperature following melatonin intake are within the normal range of circadian variation - a recognised pharmacodynamic effect of melatonin which may itself aid in the sleep-promoting effect. Whilst it appears that rare events of clinically overt hypothermia may occur in susceptible individuals, the Applicant recognises the need for harmonisation and so does not propose to include hypothermia in the SmPC section 4.8.

Nocturnal enuresis

In a systematic review of safety that included 37 RCTs [redacted] enuresis was reported in 1 study, ocurring in 3 subjects receiving melatonin.

In the literature reviewed by the applicant, increased enuresis was reported by 3/107 children [redacted] and one child terminated melatonin treatment due to bedwetting [redacted] Bedwetting was also reported during long-term melatonin treatment [redacted].

Nocturnal enuresis was improved following melatonin treatment in subjects with intractable epilepsy [redacted] or other severe handicaps [redacted] and did not affect the pattern of enuresis in a specific study of melatonin to treat nocturnal enuresis [redacted]. A study which evaluated bedwetting using a sleep difficulties questionaire also found no differences between melatonin and placebo [redacted] .

In conclusion, nocturnal enuresis was seen at 0.11-1.3% in children treated with melatonin. In most studies reporting the event, comparator data was not available. Although this event could be expected in a medication that induces sleep, there is some conflicting evidence showing no effect or improvement of nocturnal enuresis following melatonin. The Applicant recognises the need for harmonisation and so does not propose to include nocturnal enuresis in the SmPC section 4.8.

Vertigo

Vertigo was not identified as an adverse event in the Applicant's literature search. Events of light-headedness were identified in 2 subjects each in the placebo and melatonin arms of a DSWPD study [redacted] and in subjects with Parkinson's disease receiving sustained release melatonin and led to dose reduction in one patient with concurrent light-headedness and morning sleepiness [redacted] Light headedness was considered serious in 4 melatonin and 5 placebo patients [redacted]. Given the low number of events, and the similar incidence in the melatonin and placebo arms, the Applicant did not intend to include this in the list of adverse drug reactions to immediate-release melatonin. However, the Applicant recognises the need for harmonisation and so will propose to include vertigo in the SmPC section 4.8 in line with other melatonin products.

Somnolence

The morning after administration, a possible carry over effect may occur with melatonin products, particularly with prolonged release melatonin, high doses above those proposed for this product. This prolongation of supra-physiological levels has been seen in older adults causing drowsiness, somnolence, or an unsteady feeling on awakening the following day [redacted]. There is also the potential for this effect in or in patients who are poor metabolisers. However, one meta-analysis [redacted] and 4 clinical studies [redacted] found no significant negative long-term residual effects of melatonin after administration with a dosage range of 0.1 mg-100 mg in both patients with sleep disorders and healthy volunteers. In the current dossier, the incidence of daytime sleepiness or somlonence is higher for placebo than for melatonin, although the slightly higher incidence of these events compared to the current labelling for melatonin is consistent with the proposed labelling and within the expected range of variation. As most studies reported fewer or similar rates of events in the active groups compared with the placebo groups, they likely represent the background rate for the population. However, the Applicant recognises the need for harmonisation and somnolence was included in the proposed SmPC section 4.8 in line with other melatonin products.

Liver function abnormality

Liver function abnormalities of any kind were not identified as an adverse event in the Applicant's literature search. In a double-blind placebo-controlled study, no significant changes in lever parameters were observed following 10mg melatonin daily for 28 days [redacted] Indeed, melatonin is generally considered protective against liver injury [redacted] although autoimmune hepatitis has been seen in association with ramelteon [redacted]. Given the absence of events in the relevant literature, the Applicant did not intend to include this in the list of adverse drug reactions to immediate-release melatonin. However, the Applicant recognises the need for harmonisation and so will propose to include somnolence in the SmPC section 4.8 in line with other melatonin products.

Over all the indications no clear dose-relationship could be identified for safety events.

Conclusion

Most AE reported in each of the indications are background AE or AE consistent with the known safety profile of melatonin such as headaches, nausea, and diarrhoea. Overall, the proposed section 4.8 is considered appropriate and is also aligned with other currently approved melatonin preparations in the EU. However, the Applicant proposes to take a conservative approach for the paediatric population and proposes to add hypothermia and nocturnal enuresis in the SmPC section 4.8.

Table 20 Comparison of AE Literature Reports to Melatonin Labelling.

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI-COM *[n=1677-1740]*	A/CI+COM *[n=3108-4089]*	P/CI-COM *[n =201-285]*	P/CI+COM *[n = 714-867]*
Blood lymphatic disorders AEs classified as Rare							0.3 – 0.45		
Cardiac disorders AE classified as Rare						0.86 – 0.89	0.63 – 0.83		
Palpitations – Rare.	Palpitations			0.1 – 0.11					
Not listed	Palpitations in women with pacemaker						*		
Not listed	Unstable angina					*			
Not listed	Angina pectoris						0.05 – 0.06		
Congenital, familial, and genetic disorders							0.05 – 0.06		
Ear and labyrinth disorders						0.75 – 0.78	0.68 – 0.9		
Eye disorders						1.44 – 1.50			
Visnal acnity rednced or vision blnrred – Rare	Visnal distnrbances				0.13 - 0.2	0.17 – 0.18			
Gastrointestinal disorders AEs classified as Uncommon and Rare		1.3 – 2.1				13.18 – 13.66			
Vomiting - Rare	Vomiting		0.56 – 1.14	0.2 – 0.22			0.05 – 0.06		1.73 – 0.69
Nansea - Uncommon	Nansea	0.27 - 0.43	0.56 – 1.14	0.94 – 1.02	0.27 – 0.4			*	0.35 – 0.42
Not listed	Diarrhea		0.07 – 0.13	0.94 – 1.02	0.13 – 0.2	0.06 – 0.06	0.1 – 0.13		
Not listed	Constipation			1.05 – 1.13	0.13 – 0.2				
Not listed	Loss of appetite			0.94 – 1.02			0.05 – 0.06		
Abdominal Pain – Uncommon.	Abdominal Pain				0.27 – 0.4				
Upper abdominal pain - Uncommon	Epigastric pain						0.05 – 0.06		
Not listed	Abnormal feces				0.27 – 0.4				
Not listed	Bowel obstruction					*			
Not listed	Gastrointestinal distress						6.0 – 7.9	0.05 – 0.06	

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
General disorders and administration site conditions									
Not listed	Feeling cold	3.2 – 5.1						4.21 – 5.97	
Not listed	Hypothermia								0.69 – 0.84
Not listed	Incapacitation			0.1 – 0.11					
Not listed	Resistance mechanism disorders					1.27 – 1.32			
AEs classified as Uncommon and Rare	Body as a whole – general disorders					2.48 – 2.57			
Not listed	Ache/pain						*		
Not listed	Falls						0.07 – 1.0		
Not listed	Back pain						0.05 – 0.06		
Not listed	Other AE not named in pnblication						0.61 – 0.80		3.58 – 4.34
Not listed	Nose bleeding				0.13 – 0.2				
Not listed	Secondary terms					0.35 – 0.36			
Not listed	Drng related AEs						0.2 – 0.026		
Hepatobiliary disorders							0.37 – 0.5		
Immune system disorders AEs classified as Rare							7.1 – 9.4		
Infections and infestations						12.32 – 12.77			
Not listed	Inflnenza			0.1 – 0.11					
Not listed	Urinary Tract Infection						0.02 – 0.03		
Not listed	Infection						2.9 – 3.9		
Not listed	Ear infection & Bronchitis								2.5 – 3.1
Not listed	Cold/flu/infection	2.2 – 3.4				0.29 – 0.30	0.05 – 0.06		
Not listed	Appendicitis								0.11 – 0.14

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
Injnry, poisoning, and procednral complications						2.48 – 2.57	1.3 – 1.8		
Investigations AEs classified as Uncommon and Rare						1.67 – 1.73			
Metabolism and nntrition disorders AEs classified as Rare and Not known						1.09 – 1.13	4.6 - 6		
Not listed	Blood glucose increased						0.05 – 0.06		
Not listed	Sweating / profuse perspiration			0.1 – 0.11	0.13 – 0.2				
Mnsculoskeletal and connective tissne disorders AE classified as Rare						10.36 – 10.74	1.6 – 2.1		
Muscle Spasms – Rare.	Tremor		0.07 – 0.13						
Neoplasms benign, malignant and nnspecified							3.0 – 3.9		
Not listed	Thyroid neoplasm						0.02 – 0.03		
Nervous system disorders AEs classified as Common, Uncommon and Rare						5.53 – 5.73	1.8 – 2.4		
Headache - Common	Headache	0.85 – 0.85		3.25 - 3.51	0.67 – 1.0	0.58 – 0.60	0.05 – 0.06	1.05 – 1.49	1.27 – 1.54
Somnolence - Common	Daytime sleepiness	0.54 - 0.85		0.31 – 0.34					
	Fatigne/ mild fatigne	5.6 – 8.9		10.5 – 11.3			0.07 – 1.0	3.51 – 5.00	0.92 – 1.12
	Tired						0.02 – 0.03		
	Hnng-over feeling								0.11 – 0.14
	Decreased daytime alertness			0.2 – 0.22					
	Sedative effect			0.2 – 0.22					
	Daytime laziness				0.13 – 0.2				

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
	Daytime sleepiness				0.13 – 0.2				
	Drowsiness				2 (0.27%)	0.12 – 0.12			
	Excess morning sedation				2 (0.27%)		*		
	Fogginess				1 (0.13%)				
	Somnolence						0.02 – 0.03		1.04 – 1.26
	Sleep maintenance insomnia/insomnia				0.67 – 1.0		0.05 – 0.06		
Not listed	Somnambulia			0.1 – 0.11					
Not listed	Less Vigorous			0.1 – 0.11					
Dizziness and fainting – Uncommon and Rare, respectively.	Light headedness	0.54 – 0.85							
	Dizziness			1.26 – 1.36	0.9 – 1.4			4.21 – 5.97	0.11 – 0.14
Memory impairment - Rare	Memory impairment			0.2 – 0.22					
Not listed	Seizure	3.0 – 4.7							
Not listed	Depressed			0.1 – 0.11					
paraesthesia - Rare	Burning feet syndrome						0.02 – 0.03		
Mood altered – Rare.	Behavior change				0.27 – 0.4				
	Mood dips				0.4 – 0.6				1.96 – 2.38
Psychiatric disorders AEs classified as Uncommon and Rare						0.17 – 2.33	1.9 – 2.5		
Irritability, nervonsness, restlessness, anxiety - Uncommon	Agitation	1.1 - 1.7	0.03 - 0.07				0.05 – 0.06		0.11 – 0.14
	Restlessness						0.02 – 0.03		
	Increased excitability								1.5 – 1.82
Mood altered, aggressive behavionr, disorientation -	Emotional distress					0.06 – 0.06			

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
Rare	Cognitive disorder						0.02 – 0.03		
	Delusion						0.02 – 0.03		
	Decrease of mood							*	
	Abnormal behaviour						*		
Abnormal dreams– Uncommon.	Vivid dreams and/ or nightmares / Abnormal dreams	0.27 – 0.43			0.4 - 0.6		0.05 – 0.06		
Libido increased - Rare	**Decreased** libido	0.54 – 0.85							
Disorientation – Rare	Disorientation			0.52 – 0.57					
	Confused			1.05 – 1.13					
	Trouble concentrating or thinking			0.2 – 0.22					
Restlessness – Uncommon	Hyperactivity				0.4 – 0.6				0.69 – 0.84
Renal and urinary disorders AEs classified as Uncommon and Rare						3.17 – 3.28			
Not listed	High alkaline phosphatase concentration	0.54 – 0.85							
Not listed	Increased nrination/bed wetting	0.8 – 1.3			0.8 – 1.2			0.35 – 0.50 0.70 – 1.00	0.11 – 0.14
Not listed	Urinary symptoms						1.25 – 1.6		
Reprodnctive system and breast disorders Rare and Not known						1.27 – 1.32	0.63 – 0.83		
Respiratory, thoracic and mediastinal disorders						5.93 – 6.15	3.0 – 4.0		
Not listed	Cough		0.23 - 0.47				0.05 – 0.06		2.5 – 3.1
Not listed	Hiccough		0.1- 0.2						
Not listed	Difficulty swallowing			0.1 – 0.11					
Not listed	Breathing difficulty			0.1 – 0.11					0.11 – 0.14
Not listed	Upper respiratory tract infection						0.05 – 0.06		
Skin and snbcntaneons tissne disorders AEs classified as Uncommon, Rare and Not Known						3.91 – 4.06	2.18 – 2.9		

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
Rash –Uncommon.	Rash			0.1 – 0.11					1.27 – 1.54
	Painful lumps on skin				0.13 – 0.2				
	Itching lnmps on skin				0.13 – 0.2				
Dry Mouth –Uncommon	Dry Mouth			0.1 – 0.11					
Not listed	Skin pigment changes				0.4 – 0.6				
Not listed	Cellulitis					*			
Not listed	Application site disorders					0.17 – 0.18			
Surgical and medical procedures						0.46 – 0.48			
Not listed	PONV		0.03 - 0.07						
Vascular disorders AEs classified as Uncommon and Rare						1.21 – 1.25	0.73 – 0.96		

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI-COM *[n=1677-1740]*	A/CI+COM *[n=3108-4089]*	P/CI-COM *[n =201-285]*	P/CI+COM *[n = 714-867]*
Blood lymphatic disorders AEs classified as Rare							0.3 – 0.45		
Cardiac disorders AE classified as Rare						0.86 – 0.89	0.63 – 0.83		
Palpitations – Rare.	Palpitations			0.1 – 0.11					
Not listed	Palpitations iu women with pacemaker						*		
Not listed	Unstable angina					*			
Not listed	Angina pectoris						0.05 – 0.06		
Congenital, familial, and genetic disorders							0.05 – 0.06		
Ear and labyrinth disorders						0.75 – 0.78	0.68 – 0.9		
Eye disorders						1.44 – 1.50			
Visual acuity reduced or visiou blurred – Rare	Visual disturbances				0.13 - 0.2	0.17 – 0.18			
Gastrointestinal disorders AEs classified as Uucommou and Rare		1.3 – 2.1				13.18 – 13.66			
Vomiting - Rare	Vomiting		0.56 – 1.14	0.2 – 0.22			0.05 – 0.06		1.73 – 0.69
Nausea - Uucommou	Nausea	0.27 - 0.43	0.56 – 1.14	0.94 – 1.02	0.27 – 0.4			*	0.35 – 0.42
Not listed	Diarrhea		0.07 – 0.13	0.94 – 1.02	0.13 – 0.2	0.06 – 0.06	0.1 – 0.13		
Not listed	Constipation			1.05 – 1.13	0.13 – 0.2				
Not listed	Loss of appetite			0.94 – 1.02			0.05 – 0.06		
Abdominal Pain – Uncommon.	Abdominal Pain				0.27 – 0.4				
Upper abdominal pain - Uncommon	Epigastric pain						0.05 – 0.06		
Not listed	Abnormal feces				0.27 – 0.4				
Not listed	Bowel obstruction					*			
Not listed	Gastrointestinal distress						6.0 – 7.9	0.05 – 0.06	

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
General disorders and administration site conditions									
Not listed	Feeling cold	3.2 – 5.1						4.21 – 5.97	
Not listed	Hypothermia								0.69 – 0.84
Not listed	Incapacitation			0.1 – 0.11					
Not listed	Resistance mechanism disorders					1.27 – 1.32			
AEs classified as Uncommon and Rare	Body as a whole – general disorders					2.48 – 2.57			
Not listed	Ache/pain						*		
Not listed	Falls						0.07 – 1.0		
Not listed	Back pain						0.05 – 0.06		
Not listed	Other AE not named in pnblication						0.61 – 0.80		3.58 – 4.34
Not listed	Nose bleeding				0.13 – 0.2				
Not listed	Secondary terms					0.35 – 0.36			
Not listed	Drng related AEs						0.2 – 0.026		
Hepatobiliary disorders							0.37 – 0.5		
Immune system disorders AEs classified as Rare							7.1 – 9.4		
Infections and infestations						12.32 – 12.77			
Not listed	Inflnenza			0.1 – 0.11					
Not listed	Urinary Tract Infection						0.02 – 0.03		
Not listed	Infection						2.9 – 3.9		
Not listed	Ear infection & Bronchitis								2.5 – 3.1
Not listed	Cold/flu/infection	2.2 – 3.4				0.29 – 0.30	0.05 – 0.06		
Not listed	Appendicitis								0.11 – 0.14

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
Injnry, poisoning, and procednral complications						2.48 – 2.57	1.3 – 1.8		
Investigations AEs classified as Uncommon and Rare						1.67 – 1.73			
Metabolism and nntrition disorders AEs classified as Rare and Not known						1.09 – 1.13	4.6 - 6		
Not listed	Blood glucose increased						0.05 – 0.06		
Not listed	Sweating / profuse perspiration			0.1 – 0.11	0.13 – 0.2				
Mnsculoskeletal and connective tissne disorders AE classified as Rare						10.36 – 10.74	1.6 – 2.1		
Muscle Spasms – Rare.	Tremor		0.07 – 0.13						
Neoplasms benign, malignant and nnspecified							3.0 – 3.9		
Not listed	Thyroid neoplasm						0.02 – 0.03		
Nervous system disorders AEs classified as Common, Uncommon and Rare						5.53 – 5.73	1.8 – 2.4		
Headache - Common	Headache	0.85 – 0.85		3.25 - 3.51	0.67 – 1.0	0.58 – 0.60	0.05 – 0.06	1.05 – 1.49	1.27 – 1.54
Somnolence - Common	Daytime sleepiness	0.54 - 0.85		0.31 – 0.34					
	Fatigne/ mild fatigne	5.6 – 8.9		10.5 – 11.3			0.07 – 1.0	3.51 – 5.00	0.92 – 1.12
	Tired						0.02 – 0.03		
	Hnng-over feeling								0.11 – 0.14
	Decreased daytime alertness			0.2 – 0.22					
	Sedative effect			0.2 – 0.22					
	Daytime laziness				0.13 – 0.2				

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
	Daytime sleepiness				0.13 – 0.2				
	Drowsiness				2 (0.27%)	0.12 – 0.12			
	Excess morning sedation				2 (0.27%)		*		
	Fogginess				1 (0.13%)				
	Somnolence						0.02 – 0.03		1.04 – 1.26
	Sleep maintenance insomnia/insomnia				0.67 – 1.0		0.05 – 0.06		
Not listed	Somnambulia			0.1 – 0.11					
Not listed	Less Vigorous			0.1 – 0.11					
Dizziness and fainting – Uncommon and Rare, respectively.	Light headedness	0.54 – 0.85							
	Dizziness			1.26 – 1.36	0.9 – 1.4			4.21 – 5.97	0.11 – 0.14
Memory impairment - Rare	Memory impairment			0.2 – 0.22					
Not listed	Seizure	3.0 – 4.7							
Not listed	Depressed			0.1 – 0.11					
paraesthesia - Rare	Burning feet syndrome						0.02 – 0.03		
Mood altered – Rare.	Behavior change				0.27 – 0.4				
	Mood dips				0.4 – 0.6				1.96 – 2.38
Psychiatric disorders AEs classified as Uncommon and Rare						0.17 – 2.33	1.9 – 2.5		
Irritability, nervonsness, restlessness, anxiety - Uncommon	Agitation	1.1 - 1.7	0.03 - 0.07				0.05 – 0.06		0.11 – 0.14
	Restlessness						0.02 – 0.03		
	Increased excitability								1.5 – 1.82
Mood altered, aggressive behavionr, disorientation -	Emotional distress					0.06 – 0.06			

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
Rare	Cognitive disorder						0.02 – 0.03		
	Delusion						0.02 – 0.03		
	Decrease of mood							*	
	Abnormal behaviour						*		
Abnormal dreams– Uncommon.	Vivid dreams and/ or nightmares / Abnormal dreams	0.27 – 0.43			0.4 - 0.6		0.05 – 0.06		
Libido increased - Rare	**Decreased** libido	0.54 – 0.85							
Disorientation – Rare	Disorientation			0.52 – 0.57					
	Confused			1.05 – 1.13					
	Trouble concentrating or thinking			0.2 – 0.22					
Restlessness – Uncommon	Hyperactivity				0.4 – 0.6				0.69 – 0.84
Renal and urinary disorders AEs classified as Uncommon and Rare						3.17 – 3.28			
Not listed	High alkaline phosphatase concentration	0.54 – 0.85							
Not listed	Increased nrination/bed wetting	0.8 – 1.3			0.8 – 1.2			0.35 – 0.50 0.70 – 1.00	0.11 – 0.14
Not listed	Urinary symptoms						1.25 – 1.6		
Reprodnctive system and breast disorders Rare and Not known						1.27 – 1.32	0.63 – 0.83		
Respiratory, thoracic and mediastinal disorders						5.93 – 6.15	3.0 – 4.0		
Not listed	Cough		0.23 - 0.47				0.05 – 0.06		2.5 – 3.1
Not listed	Hiccough		0.1- 0.2						
Not listed	Difficulty swallowing			0.1 – 0.11					
Not listed	Breathing difficulty			0.1 – 0.11					0.11 – 0.14
Not listed	Upper respiratory tract infection						0.05 – 0.06		
Skin and snbcntaneons tissne disorders AEs classified as Uncommon, Rare and Not Known						3.91 – 4.06	2.18 – 2.9		

AEs in SmPC Section 4.8 (and Freqnency)	Event term	Incidence (%)							
		DSWPD *[n=235-372]*	Sedation *[n=1486-3019]*	Jet lag *[n=884-953]*	P/CI in ADHD *[n=495-746]*	A/CI -COM *[n=1677-1740]*	A/CI +COM *[n=3108-4089]*	P/CI -COM *[n =201-285]*	P/CI +COM *[n = 714-867]*
Rash –Uncommon.	Rash			0.1 – 0.11					1.27 – 1.54
	Painful lumps on skin				0.13 – 0.2				
	Itching lnmps on skin				0.13 – 0.2				
Dry Mouth –Uncommon	Dry Mouth			0.1 – 0.11					
Not listed	Skin pigment changes				0.4 – 0.6				
Not listed	Cellulitis					*			
Not listed	Application site disorders					0.17 – 0.18			
Surgical and medical procedures						0.46 – 0.48			
Not listed	PONV		0.03 - 0.07						
Vascular disorders AEs classified as Uncommon and Rare						1.21 – 1.25	0.73 – 0.96		

* n = not specified

Deaths

No deaths were reported in the publications reviewed. While high melatonin plasma levels in deaths of undetermined causes have been reported in the USA, no causal link has been identified [redacted].

Other Serious Adverse Events

[redacted] stated serious AEs were very rarely reported and were, in most cases, either an exacerbation of a pre-existing condition (e.g. worsening migraine), characteristic of the study population (e.g. agitation and mood swings in patients with ADHD, ASD or other developmental or behavioural disorders), or more severe episodes of otherwise commonly reported AEs (e.g. fatigue, nightmares and skin irritation). Further reports of serious AEs were described in 2 of the supplementary papers [redacted] and these have been tabulated in Section 2.7.4.2.3.

Adverse Events leading to Withdrawal

In patients receiving immediate release melatonin treatment across all studies reviewed, discontinuations were rare with incidences from studies that reported safety data of <1% in all indications (a higher rate was seen with sustained release melatonin for chronic insomnia in adults). From the reported IR melatonin studies there were 7 withdrawals associated with the treatment group reporting the specific adverse event leading to discontinuation as excessive drowsiness (2), bedwetting (1), nausea (1), difficulty swallowing/breathing (1), aggressiveness (1) and nightmares (1). In summary, only transient, non-serious adverse events leading to discontinuation were reported in patients that underwent treatment with melatonin. The incidences of AEWD were similar in the melatonin and placebo treatment groups. The most common adverse event leading to discontinuation was daytime sleepiness or somnolence. Events of drowsiness the next day may be more appropriately treated in clinical practice by use of an IR formulation in patients previously taking a PR formulation, or by an reduction of the dose of IR melatonin to ensure melatonin levels return to normal by daybreak.

These figures support the overall conclusion that melatonin is a generally safe molecule with an AE profile that is both limited and mild.

Adverse Events by Syndrome

The common serious AEs reported by syndrome in this section of the overview are tabulated in the section on Adverse Events in Section 5.1 above in Table 19.

Unwanted Efficacy

From the publications reviewed for safety, unwanted efficacy was reported with effects including dizziness, daytime sleepiness muzziness /funny feeling /hungover, other sleep related AEs, fatigue and hypothermia. These effects were more common with PR formulations or high doses.

Return of symptoms or rebound on discontinuation

From the publications reviewed for safety, effects of restlessness /agitation, hyperactivity, insomnia and tearfulness were reported.

Gastrointestinal

From the publications reviewed for safety, gastrointestinal events were reported with effects of decreased appetite, burping and other-gastrointestinal illness or diarrhoea.

Skin

From the publications reviewed for safety, rashes were reported in a few studies including any skin irritation, pruritus or itching.

Seizures

Seizures were reported in 2 studies. [redacted] reported no evidence of an increased risk of seizures in any of the subjects who participated in the RCTs included in its review. The supplementary studies identified one RCT [redacted] evaluating the efficacy and safety of oral melatonin in children for the prevention of recurrent simple febrile seizures. The authors suggested that melatonin, administered at the onset of a febrile illness, may effectively reduce the likelihood of recurrent simple febrile seizures.

Melatonin has been reported to increase, decrease and have no effect on seizure frequency. Because of the uncertainty of the effect of melatonin on epileptic seizures, some caution should be exercised for use in people with epilepsy.

Reproductive and Endocrine Effects

Sixteen of the RCTs reviewed by [redacted] included subjects of pre-pubertal age. However, none were of sufficient duration to detect anything but the most acute effects. A 1-week dose-finding RCT led into a long-term observational phase in which Tanner stages were assessed in comparison with healthy controls. No significant differences were detected during the initial trial or follow-up period.

No clear evidence that exogenous melatonin interferes with normal pubertal development in humans was found in these studies, but the scarcity of long-term RCTs in children and adolescents implies that there are very limited data available. The current absence of substantial confirmatory data on long-term safety in pre-pubertal children has led to a consensus that melatonin should not be recommended as a first-line treatment for chronic sleep disorders in this population. However, this recommendation appears to be based on lack of data rather than firm evidence for an effect of melatonin on puberty [redacted]. The impact of melatonin on fertility and puberty in animals that are seasonal breeders is discussed in Module 2.4 but is not directly relevant in humans.

The scarcity of data on the interaction between melatonin and growth hormone, and the effect of exogenous melatonin on normal growth hormone profiles, means that any possible consequence of long-term exposure to supranormal melatonin levels remain unclear.

Diabetes, Glucose Tolerance and Insulin Resistance

A placebo-controlled cross-over study of diabetic patients with insomnia taking 2-mg/day prolonged-release melatonin showed no adverse effect on glucose or lipid metabolism during a 3-week RCT and 5-month open-label follow-up. Furthermore, glycaemic control showed improvement over the course of long-term melatonin therapy. The only other RCT including diabetic patients in [redacted] found no AEs but was not focused on detecting the influence of melatonin on metabolic symptoms.

Only a small number of RCTs investigating the effect of melatonin therapy on the symptoms of diabetes and metabolic syndrome has been published. In the absence of clear evidence, individuals with pre-existing diabetes, metabolic syndrome or glucose intolerance should be monitored for any possible metabolic effects of melatonin [redacted].

Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. Ceyesto 1 mg/ml Oral Solution should be taken at least 2 hs before and at least 2 hs after a meal; ideally at least 3 hs after meal by persons with significantly impaired glucose tolerance or diabetes. (Refer to Extrinsic factors described in Section 3.1 Pharmacokinetics).

Respiratory

Asthma was present in subjects in three RCTs included in the review of [redacted] No evidence of either worsening or improvement in asthma symptoms was reported. Improvements in sleep quality have been observed in patients with asthma treated with melatonin, even where no

evidence of a positive effect on asthma severity, use of relief medication or peak expiratory flow rate was found. This indicates no special safety precautions are reported in patients with asthma.

Autoimmune

In the studies summarised in this overview of safety, there were no patients reported with exacerbation of autoimmune disease. Additional search terms were applied to [redacted] to identify any publications on immunogenicity of oral melatonin and no additional publications were identified on the immunogenic effects of melatonin indicating there is a low potential for hypersensitivity from the literature search. However, occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin while others have reported beneficial effects of melatonin [redacted]

Seven clinical studies indicate the potential for melatonin to have immunomodulatory effects in autoimmune disease [redacted] in rheumatoid arthritis, [redacted] in myasthenia gravis, [redacted] in ulcerative colitis, [redacted] in haemodialysis, [redacted] in Parkinson'sdisease, [redacted] in cancer). While beneficial effects can be seen on some disease outcomes, proinflammatory laboratory changes were also observed, although these had no overt clinical sequelae. In contrast to the broadly positive picture from clinical studies, negative outcomes in autoimmune disease have been reported in occasional individual case reports in myasthenia gravis and in autoimmune hepatitis.

Three case reports describe a temporal relationship between the start of melatonin therapy and worsening of MG. However, the interpretation of the potential safety signal is complicated by a number of factors. There is no significant improvement in the patients' status on dechallenge when melatonin is stopped. In all 3 cases the worsening of MG is responsive to increase or reinstatement of therapy for MG. The total number of MG patients followed by the clinic is not given, and neither is the number taking melatonin. Therefore, the relative rate of worsening in MG patients taking melatonin cannot be calculated, and cannot be compared with the background rate of exacerbations of MG.

Three cases show a temporal relationship between the use of melatonin or a melatonin agonist at normal therapeutic doses and the development of autoimmune hepatitis. In one case a classic dechallenge – rechallenge was achieved, strongly suggesting a direct causal link with melatonin treatment. The single fatal case was observed with ramelteon rather than melatonin, but does raise the possibility that a rare side effect of autoimmune hepatitis may be a class effect for melatonin and melatonin agonists.

Due to the sparse and conflicting data Ceyesto 1 mg/ml Oral Solution is not recommended in patients with autoimmune diseases.

<u>Special Populations</u>

Age

From the studies identified, 3 studies [redacted] investigated the safety and efficacy of melatonin, primarily in elderly patients with insomnia. [redacted] reported AE rates were generally similar in the prolonged release melatonin (PRM) and placebo treatment groups (aged 18-80 years). The authors stated there was no evidence of a difference between treatments or age groups in the type and amount of AEs. [redacted] concludes their study demonstrated short- and long-term safety of melatonin in elderly insomnia patients. [redacted], reported the safety and efficacy of melatonin (utilising the same patient data as [redacted] between the 2 subsets of patients aged 18-54 and 55-80 years old. No

withdrawal symptoms or rebound insomnia were detected. [redacted] reiterate their results demonstrate short- and long-term efficacy of PRM in insomnia patients aged 18–80 years, particularly those aged 55 and over. PRM was well-tolerated over the entire 6-month period with no rebound or withdrawal symptoms following discontinuation. [redacted] investigated melatonin (as a food supplement) in patients aged 78.3 ± 3.9 years with primary insomnia and reported the melatonin as safe and well tolerated.

Comparison of paediatric and adults studies did not suggest any meaningful difference inn the safety profile with age.

Additional analyses to support safety during growth and sexual maturation were conducted and are reported in Module 2.7.4. Safety in children below 6 years is discussed in the context of the paediatric indications proposed, and in paediatric subjects reported in other literature.

Safety in children and adolescents - Puberty and development

Melatonin is widely considered to be a safe and effective medication to treat sleep disturbances in children and adolescents. The concern regarding exogenous melatonin and the potential impact on growth and puberty are predominantly based on the extrapolation from a variety of animal studies, as melatonin has been shown to regulate pubertal development in some juvenile mammalian species. In seasonal breeders, melatonin seems to act as either pro-gonadotrophic or as anti-gonadotrophic according to the period of the year - autumn-winter/short days or spring-summer/long days respectively (Module 2.4.4.5) and indicates a low potential for reproductive and developmental toxicity, with some effects on the timing of sexual development: 100µg of subcutaneous melatonin in rat pups advanced vaginal opening in 5-day-old pups, but this was delayed in 10-day-old pups [redacted] with similar results showing precocious puberty and an increase in the number of oestrous smears following a single subcutaneous injection of melatonin in 5-day-old female Wistar rats [redacted]

A progressive reduction in serum melatonin levels with increasing age, suggest a possible role of melatonin in puberty [redacted] with found lower serum levels of melatonin in children with precocious puberty [redacted] and increased serum melatonin in males with hypogonadotropic hypogonadism and delayed puberty [redacted] However, several other studies tend to suggest that decline of serum melatonin levels is simply a reflection of a general trend of age-related decrease in melatonin concentrations starting from early childhood to old age and has no relationship to puberty or precocious puberty [redacted]. The reduction in melatonin levels may also be a secondary effect of the hormonal changes happening during puberty.

There is some suggestion that the administration of exogenous melatonin may lead to supraphysiological levels in pre-pubertal and pubertal children, that could, in turn, have the potential to lead to pubertal abnormalities. However, as most data is obtained in seasonal breeders this is not considered to be an established neuro-endocrine model of puberty in humans, as humans are not seasonal breeders and the light and day length does not play a role in human puberty. Secondly, the experimental perturbations of melatonin levels in animal studies have not been physiological, either in the amount of melatonin or timing of effect. Additionally, the results from animal studies under these conditions are inconsistent, while sheep and hamsters have been affected under these conditions, other animals observed under this artificial stimulus have not shown an alteration in pubertal development. For example, [redacted] demonstrated that melatonin implants in gilts did not alter oestrogen feedback or demonstrate an advance on puberty. Therefore, the relevance to humans is unclear, and extreme caution should be exercised in the extrapolation of non-clinical data from animal models to man.

An effect on human endocrine function by exogenous melatonin has been demonstrated in adult women by [redacted] with the use of extremely high dose melatonin (300mg) in

combination with norethisterone as a potential contraceptive (n=12; aged 18-37 yr) over 4 months, resulting in a reduction in blood levels of luteinising hormone and progesterone. However, the dose utilised was approximately 50-100 times higher than the doses utilised for sleep disorders and melatonin was administered during the day, rather than in concert with the nocturnal rise in endogenous melatonin production. As such the results from this study should be reviewed with caution when considering the proposed product / indications.

No clear evidence that exogenous melatonin interferes with normal pubertal development was found in the studies in humans in the current review, but the data are limited as long- term RCTs in children and adolescents are not generally acceptable or feasible. All studies included in this submission that included treatment of children with melatonin for 6 months or more are summarised in Module 2.7.4. Out of the 33 publications, more than 1000 children were evaluated. Thirty publications did not report a significant adverse effect on puberty and development - 10 specifically investigated or discussed the effects of melatonin on puberty and development. Two long-term follow up studies [redacted] reported potential concerns related to an impact on pubertal development although there were clear confounding factors. The clinical review by [redacted] reported that the impact of melatonin on puberty is inconclusive. The remaining 7 studies reported no significant differences in sexual development or detrimental impact on growth and puberty in patients treated with melatonin.

[redacted] conducted a 3-year follow-up assessment of a RCT and reported, out of 94 children with ADHD and sleep disorders, that 2 children discontinued treatment due to concerns regarding the long-term treatment on pubertal development. The age of the children that discontinued was not stated and no specific adverse events were reported in relation to puberty. No further information was reported in regard to these 2 patients. The authors concluded that the effects of long-term use of melatonin on pubertal development could not be properly assessed within the constraints of the study design, and that there is no clinical or research evidence after so many years that exogenous melatonin significantly influences the onset of human puberty.

[redacted] followed subjects who had participated in a melatonin dose-finding trial [redacted] to establish whether long-term use of melatonin influences pubertal development, sleep quality and mental health development in children as compared with the normal Dutch population of the same age. In the original trial, eligible participants were children aged between 6 and 12 years who were in good general health, otherwise suffering from sleep onset insomnia more than four nights a week for more than 1 year, based on parental reports. In addition, this initial study found no significant differences in sexual development, weight or height compared with age-matched and gender-matched controls. At initial follow-up by questionnaire, the mean age of the remaining 57 children was 12.0 (min 8.6, max 15.7 years). Melatonin was still used by 48 children at the time of questioning, mean duration of use was 3.1 years (min 1.0, max 4.6 years) and mean dose was 2.7 mg (min 0.3, max 10 mg). Mean SDQ score, mean CSHQ score and Tanner Stages standard deviation scores did not differ in a statistically significant way from published scores of the general Dutch population of the same age and sex. The authors concluded that this follow-up study demonstrates that melatonin treatment in children can be sustained over a long period of time without substantial deviation of the development of children with respect to sleep quality, puberty development and mental health scores, as compared with the general Dutch population.

A further follow-up study, completed by [redacted] in the same study population was on average ten years after treatment initiation, with 33 participants responding (age range 16.7 to 23.2 years [mean 19.6 years]). Nine respondents (27.3%) still used melatonin after an average treatment duration of 10.8 years. The overall average treatment duration was 7.1 years. Assessment of perceived pubertal timing was evaluated with one questionnaire item derived from the Puberty Development Scale (PDS), by which participants were asked to indicate whether they felt their timing of pubertal development was any earlier or later than most other

boys or girls of the same age. Results were compared with data from [redacted], who reported on perceived pubertal timing in a population of 8951 Norwegian adolescents and young adults aged 13–19. Perceived pubertal timing was at about the same time as that of their peers for 50% of the study population. Overall, 31.3% of 33 patients self-identified as having experienced delayed puberty. However, it should be noted that the population of patients who receive melatonin is not a direct match for the general population due to the higher proportion with comorbidities such as neurodevelopmental disorders.

Although, [redacted] reported that more participants perceived pubertal timing as late as compared to controls of the same age, indicating a possible tendency towards delayed puberty in former and current users of melatonin, the authors warned that one should be careful when interpreting these results, as perceived pubertal timing is only indicative of and not directly related to the actual timing of pubertal development. Also, perceptions about pubertal timing results are known to be dependent on the age of assessment and to vary during maturation. The authors concluded that to which extent these subjective results indicate an actual delay in onset of puberty as a result of melatonin treatment in early childhood is inconclusive. In addition, the authors stated that melatonin therapy sustained for 7.1 years does not result in substantial deviations of sleep quality as compared to controls and appears to be safe.

[redacted] reported consecutive findings from a group of children with autism spectrum disorder or other NDD who initiated melatonin in a 13-week randomized, parallel group, double blind, multicentre, placebo-controlled trial (n=125; 2-17.5 years of age) with the last assessment by [redacted] which assessed sleep, growth, and puberty after two years of prolonged-release melatonin (106 weeks, 80 children aged 2-17.5 years). Changes in mean weight, height, body mass index, and pubertal status (Tanner staging done by a physician) were within normal ranges for age with no evidence of delay in body mass index or pubertal development. Long-term follow-up data showed maintained efficacy with improvements in child sleep disturbance and caregiver satisfaction with child sleep patterns, quality of sleep, and quality of life were maintained throughout the 104-week treatment period ($p<.001$ versus baseline for all). In addition, there were no observed detrimental effects on children's growth and pubertal development, and no withdrawal or safety issues related to the use or discontinuation of the drug. The authors concluded that prolonged-release melatonin at optimal dose (2, 5, or 10 mg nightly) is safe and effective for long-term treatment in children and adolescents with autism spectrum disorder and insomnia.

[redacted] reported in an open label follow-up of subjects enrolled in a placebo-controlled, double-blind cross-over trial of sustained-release melatonin, that the onset of puberty was found to be age appropriate in all but five of 41 children with neurodevelopmental disabilities taking melatonin for sleep disorders for periods of up to 9.6 years (mean duration of 4.3 years). The five remaining children all displayed signs of precocious puberty prior to the start of melatonin therapy. None (0/41) of the caregivers surveyed reported side effects attributed to therapy.

[redacted] reviewed the evidence for effects on puberty. Sixteen of the RCTs reviewed included subjects of pre-pubertal age. However, none were of sufficient duration to detect anything but the most acute effects. A 1-week dose-finding RCT led into a long-term observational phase in which Tanner stages were assessed in comparison with healthy controls. No significant differences were detected during the initial trial or follow-up period. No clear evidence that exogenous melatonin interferes with normal pubertal development in humans was found in these studies.

In addition to clinical trial data, there is substantial exposure to melatonin through clinical use in children. Off-label use in paediatrics has been going on for some time which mirrors the situation in the UK. As a consequence of this long-established prescribing behaviour with melatonin, an extensive amount of patient exposure in paediatric populations must have already occurred without any significant safety signals including for delay to puberty being raised.

The EudraVigilance Data Analysis system (EVDAS) is a database maintained by the EMA which collects details of all reported adverse events. It can be searched in a multitude of ways including looking at a particular drug substance, indication, adverse event etc. This means that search results from EVDAS can provide a comprehensive overview of the safety of a particular product, substance or indication as well as the prevalence of a particular side effect.

[redacted] In addition, the safety of melatonin in general can be put into further context when one considers the safety profile of benzodiazepines and zolpidem (both used in sleep indications).

[redacted].

As such the search of the [redacted] supports both the overall safety profile of melatonin and the conclusion that the risk of delay in puberty / sexual maturation in children and adolescents with melatonin is a theoretical rather than an actual risk, particularly when set against the background rate of these disorders.

It should also be recognised that the above mentioned 'off-label' use in the UK has not manifested in an absence of monitoring by healthcare organisations or a lack of knowledge around the theoretical risk. Indeed the risk of delay in sexual maturation (puberty) is already included in the majority of NHS Shared Care Agreements with most of these outlining monitoring responsibilities in Primary and Secondary care.

It is evident from all of the above that the theoretical potential risk with regards to melatonin and sexual maturation / puberty is well understood by the healthcare community in the UK with clear published clinical guidance for the monitoring of patients and yet this has not manifested in any way in terms of an increased prevalence or reporting of incidents. This provides further clear support for the conclusions drawn from the literature that the risk for delay in puberty from melatonin is theoretical in nature and of very low risk.

Conclusion – Delayed Sexual Maturation in Children / Adolescents

Overall, the studies examined in this submission that assessed children and adolescents for 6 months to 10 years after treatment initiation do not demonstrate a conclusive, significant detrimental impact or interference to normal puberty and development. No significant differences were detected during the initial trial phase or extended follow-up periods utilised by these studies, or on comparison to control populations. The tendency towards self-reported delayed pubertal timing identified in one study was determined by the authors to be inconclusive [redacted] Similarly, the signs of precocious puberty reported in one study were identified in all 5 children prior to the start of treatment with melatonin [redacted] and although [redacted] reported that 2 children discontinued treatment due to concerns regarding the long-term

treatment on pubertal development, no specific adverse events were reported in relation to puberty.

While there is a potential theoretical risk of pubertal irregularity as a consequence of supraphysiological levels of melatonin in pre-pubertal and pubertal children, the risk is low in the intended paediatric populations due to the low physiological levels of melatonin in these patient groups with sleep disturbances. The administration of low supplemental doses of melatonin in these patient populations, as described in the proposed SmPC, is intended to align with the physiological timing of endogenous melatonin release.

Furthermore, the post-marketing data reported by [redacted] for an immediate-release melatonin formulation [redacted] used in the UK since 2008 as an unlicensed medicine for sleep disturbance in children, recorded no adverse events to date on sales of approximately 600,000 packs, equivalent to some 35 million individual 3 mg tablet doses (MHRA yellow card adverse event recording scheme). This is further supported by the results of the above mentioned [redacted] which returned 2 results that *could* be related to this potential risk out of 2533 overall cases (0.079%). In conclusion, it has been demonstrated that melatonin treatment in children can be sustained over long periods of time without substantial deviations in development with respect to sleep quality and puberty development.

Despite the overall conclusion of both the Applicant and EMA that melatonin cannot have any great impact on pubertal development and as mentioned in the executive summary part of this response, the Applicant is proposing additional pharmacovigilance activities and routine risk minimisation measures in the risk management plan (RMP) which are considered sufficient to monitor the risk whilst taking account of the overall conclusion (which is supported both by studies and overall safety data) that melatonin does not have any great impact on pubertal development.

Renal and Hepatic Impairment

In the studies summarised in this overview of safety, there were no patients with renal or hepatic impairment reported as using melatonin. The limited data available on the safety of melatonin in patients with renal impairment or hepatic impairment suggests it is not recommended for use in patients suffering from severe renal impairment or moderate or severe hepatic impairment.

Hypertension

From the studies identified from Section 4.1 (Overall Efficacy), one study [redacted] investigated the efficacy and safety of prolonged release melatonin for primary insomnia, in patients aged 55 years and older who were treated with antihypertensive drugs. The authors reported the safety profile of prolonged release melatonin in this population was benign compared with placebo and appears to be safe for insomnia in patients with cardiovascular comorbidity.

Cancer Patients

From the studies identified from Section 4.1 (Overall Efficacy), 1 study [redacted] investigated melatonin in cancer patients and reported that they did not observe any adverse effects of melatonin treatment.

Pregnancy and Lactation

The systematic literature review identified one phase 1 trial [redacted] that reported the administration of exogenous melatonin to 20 pregnant women for preeclampsia. The authors reported that melatonin therapy was safe for mothers and their foetuses. Furthermore, [redacted] and [redacted] conducted in-vitro studies and reported melatonin could be considered as an effective antioxidant treatment for preeclampsia.

However, at this moment, exogenous melatonin should not be administered during pregnancy due to the lack of sufficient human studies supporting either clinical effects or risk of adverse effects [redacted]).

Experimental studies in vitro and in vivo indicate that melatonin is instrumental to optimal ovarian and placental function. Seven studies were identified as investigating the effects of melatonin on in vitro fertilization (IVF) [redacted] These studies reported melatonin had significantly higher fertilization rates or reported improved oocyte / embryo quality. The preliminary studies investigating in vitro fertilization treatments reported improved pregnancy rates after the administration of 3 mg of melatonin daily [redacted]

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

Four studies analysed male sperm quality and sperm apoptosis with melatonin [redacted]. The authors reported improved sperm quality and that melatonin reverses sperm apoptosis due to its free radical scavenging actions.

Two studies reported exogenous melatonin positively influenced quality of blastocysts in in vitro maturation [redacted]

In addition, in human placental choriocarcinoma cell line, melatonin increased autophagy whereas in isolated human primary villous cytotrophoblasts from normal term placenta it was reported as cytoprotective [redacted]. Another study reported a protective effect of melatonin to the placenta and foetus from isolated placental cytotrophoblasts [redacted] reported an antiproliferative action of melatonin in embryonal carcinoma stem cells.

In-vitro development of human embryos with culture medium fortification with melatonin was investigated by [redacted]. The authors reported melatonin had prolonged survival time of human embryos.

Overall, the studies identified melatonin as positively supporting fertilisation and foetal development, however, further high-quality research is needed in this patient sub-group.

Overdose

Melatonin overdose is rare but can occur, particularly in countries where melatonin is less regulated. A report from the American Association of Poison Control Centers' National Poison Data System (NPDS) over a 10-year study period included 260,435 pediatric melatonin ingestions. Five children required mechanical ventilation, and two died although no causal links specifically to melatonin were confirmed [redacted].

Drowsiness, headache, dizziness, and nausea are the most commonly reported signs and symptoms of overdose with oral melatonin.

Ingestion of daily doses of up to 300 mg of melatonin did not cause clinically significant adverse reactions.

Flushes, abdominal cramps, diarrhoea, headache, and scotoma lucidum have been reported after ingestion of extremely high melatonin doses (3000 – 6600 mg) for several weeks.

General supportive measures should be employed. Gastric lavage and administration of activated charcoal can be considered.

Clearance of the active substance is expected within 12 hs of ingestion.

Driving and using machines

Melatonin has a moderate influence on the ability to drive and use machines. Melatonin may cause drowsiness and may decrease alertness for several hours, therefore use of Ceyesto 1mg/ml Oral Solution is not recommended immediately before driving and using machines.

5.2 Post-Approval / Marketing Experience

Ceyesto 1 mg/mL Oral Solution is not currently marketed however, melatonin is a well-established active substance, with recognized efficacy and acceptable safety, and has been licensed in the EU for more than 15 years.

The national Prescribing Cost Analysis (PCA) data presented below is taken directly from Open Prescribing's interactive tool and shows items dispensed in the community in England. All figures are adjusted for England's population size and costs are corrected for inflation by the tool. The term 'Items' is the number of times a product appears on a prescription form. In 1998 there were 497,000 items which had almost doubled by 2011, demonstrating a continued and significant use of melatonin products in England (and the UK)[redacted]

Melatonin oral preparations were the most frequently notified unlicensed imported medicine from 1 October 2018 to 31 December 2018 with 2,910 notifications. They accounted for 12.85% of all unlicensed imported medicines notified to the MHRA. This was despite the availability of melatonin in licensed forms. Melatonin items have remained consistently within the top 5 of licensed imports with 49,819 items being imported into the UK in 2020.[redacted].

Extensive prescribing of melatonin in the UK as described above has not resulted in any signals being seen[redacted] across Europe either for any licensed form of melatonin. It should also be recognised that this is not due to an absence of monitoring by healthcare organisations which could have been argued to be the case due to the off-label nature of use. The theoretical risk of delay in sexual maturation (puberty) is already included in the majority of NHS Shared Care Agreements with the most of these outlining monitoring responsibilities in Primary and Secondary care. It is therefore evident that the theoretical potential risk with regards to melatonin and sexual maturation / puberty is well understood by the healthcare community in the UK (and across Europe) with clear published clinical guidance for the monitoring of patients. However there has not been any increased prevalence or reporting of incidents as might be expected (Weber effect / notoriety effect). This provides further clear support for the conclusions drawn from the literature that the potential for delay in puberty from melatonin is theoretical in nature and of very low risk.

Furthermore, the post-marketing data reported by[redacted] for an immediate-release melatonin formulation[redacted] used in the UK since 2008 as an unlicensed medicine for sleep disturbance in children, recorded no adverse events to date on sales of approximately 600,000 packs, equivalent to some 35 million individual 3 mg tablet doses (MHRA yellow card adverse event recording scheme). In conclusion, it has been demonstrated that melatonin treatment in children can be sustained over long periods of time without substantial deviations in development with respect to sleep quality and puberty development.

The combination of the extensive exposure to melatonin and the scarce safety reports underline the good safety profile of melatonin during clinical use for the well-established indications.

5.3 Safety Summary and Conclusions

Melatonin has been studied in a broad range of patients and at a wide range of doses. It has been found to be safe with very few adverse events recorded and with a favourable side effect profile. It has minimal or positive impacts on daytime performance and alertness when taken as directed. Side effects resolve on cessation of the medication and there is no evidence of any long term side effects. In conclusion, melatonin is a safe medication when taken in the appropriate manner with an excellent benefit to side effect ratio.

6. BENEFITS AND RISKS CONCLUSIONS

This Clinical Overview supports an application for marketing authorisation of Melatonin 5 mg/5 mL oral solution according to Article 10(1)(a)(ii) of Directive 2001/83/EC.

Melatonin is a well-established active substance, with recognized efficacy and acceptable safety, and has been licensed in the EU for more than 15 years. Melatonin is a naturally occurring hormone produced by the pineal gland and released into the bloodstream exclusively at night following the circadian rhythm. The physiological actions of melatonin are mediated by two G-protein coupled membrane receptors, MT1 and MT2, and the MT3 binding site. The majority of the high-affinity MT1 and MT2 receptors are expressed in the suprachiasmatic nucleus (SCN) and have distinct functional roles in sleep regulation. Activation of the MT1 receptor suppresses neuronal firing rate in the SCN, while MT2 acts mainly by inducing circadian rhythm phase shifts.

The intent of treatment with Ceyesto, as an immediate release melatonin formulation, is to target sleep processes within the first few hours after administration. The primary targets are correction of any misalignment of the circadian rhythm (chronobiotic effect) and support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect). These effects are similar across all sleep disorders and populations.

The chronobiotic effect of melatonin to reset the circadian rhythm is driven by increasing the melatonin level up to 7 hours before the endogenous dim light melatonin onset (DLMO). This is the most important component of efficacy in DSWPD and jet lag. The chronobiotic effect also contributes to the effect of melatonin in sleep onset insomnias with a delayed DLMO. A change in DLMO therefore provides a robust objective marker of efficacy in patients where DLMO is misaligned at baseline.

The hypnotic effect of immediate release melatonin peaks swiftly after administration, closely following plasma levels. Melatonin is intended to improve the patient's ability to fall asleep with the time of sleep onset, and the sleep onset latency, considered the key clinical parameters. The subtypes of insomnia where immediate release melatonin is expected to be effective are those which include difficulty or delay in initiating sleep. During the early hours of the night, sleep maintenance and sleep quality may also be improved, but this is difficult to measure independently from the total sleep experience across the night. Total sleep time may also be improved where it was impacted by the difficulty falling asleep. In general, patients receiving immediate release melatonin would be expected to awake at the same time or earlier, as they may have completed their natural sleep cycle earlier. Immediate release melatonin is not expected to have any effect to prolong sleep during the early morning hours and patients where the predominant complaint includes waking in the early hours of the morning are not expected to benefit from immediate release melatonin. However, it should be noted that in patients with impaired clearance of melatonin such as some elderly patients, higher levels, and hence improvement of sleep, may persist throughout the night. The hypnotic effect of melatonin is the main effect in the induction of sedation.

The first approvals for melatonin in the EU as a medicinal product were in Poland and Hungary in 2001 and 2003 respectively followed by the EU wide approval of Circadin in 2007 and further

multiple approvals. Overall, melatonin has been in safe and effective use for the requested indications for well over 10 years as described in Module 2.7.3 and Module 2.7.4. In the clinical use of melatonin there is a well-established practice of crushing modified release tablets both for administration via enteral feeding tubes but also to provide an immediate release formulation for the treatment of sleep onset insomnia, these aspects have also been considered where approproriate to this application. A significant degree of off-label use is prevalent with melatonin as shown by the prescribing data and clinical guidelines described in Module 2.7.3. The Applicant's submission is clinically justified and approval will provide an improvement in prescribing and patient safety. The extent of use on a geographical basis for over 10 years fulfils the requirements of Article 10(1)(a)(ii) of Directive 2001/83/EC. The submitted package of bibliographic data is considered sufficient to conclude that there is a high level of scientific interest and that melatonin is effective in the proposed indications.

Melatonin pharmacokinetics displays high inter-individual variability. Overall, the inter-individual variability has been estimated to be 50-70 % and the intra-variability at ~30-50%. The individual differences in circadian rhythm, absorption, distribution, metabolism and elimination between subjects contribute to the variability reported.

The absolute oral bioavailability of melatonin is poor, reported values range from 3 to 76%. Following administration of oral immediate-release formulations of melatonin, Tmax is approximately 50 min (reported values ranged from 15 (dose: 2 mg) to 90 min (dose: 25 mg), Cmax ranged from 170 (dose: 0.3 mg) to 101163 pg/mL (dose: 100 mg). Elimination half-life t1/2 is about 45 min (reported values ranged from 32 (dose: 2 mg) to 126 min (dose: 4 mg). Following oral administration, Cl/F ranged from 1.63 (dose: 6 mg) to 132.50 L/min (dose: 6 mg), volume of distribution (oral) (VD/F) ranged from 451 (dose: 5 mg) to 1602 L (dose: 4 mg). Prepubertal subjects (mean age, 8.4 years) displayed significantly shorter t1/2 and a lower AUC compared to adult subjects. Critically ill patients displayed accelerated absorption and compromised elimination. Melatonin pharmacokinetics is affected by caffeine, smoking, oral contraceptives, feeding status, and fluvoxamine.

Melatonin is primarily eliminated by hepatic metabolism, principally by 6-hydroxylation, with O-demethylation representing a relatively minor pathway. The resulting 6-hydroxymelatonin and N-acetyl-5-hydroxytryptamine (N-acetylserotonin) are excreted in urine as their sulfate and glucuronide. Only 0.01% of ingested melatonin is excreted into urine unchanged. CYP1A1, CYP1A2, CYP2C19, and CYP1B1 seem to be involved in the metabolism of melatonin, the most important being CYP1A2 enzyme. Indeed, patients with reduced CYP1A2 capacity may be more at risk from side-effects of prolonged release melatonin. About 60-80% of melatonin is reversibly bound to plasma albumin with a low binding affinity.

In children of 6 to 12 years, with ADHD and chronic sleep onset insomnia melatonin advanced sleep onset by 26.9 ± 47.8 minutes, compared to a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$) in a 4-week randomised, double-blind, placebo- controlled study. In the melatonin group an advance of sleep onset >30 minutes was more common (48.8% of children) than in those who received melatonin (12.8%, $p = 0.001$).

In randomised controlled studies of melatonin in children and young adults with DSWPD, melatonin treatment significantly reduced sleep onset latency and / or sleep onset time and advanced DLMO, a marker of circadian rhythmicity.

The efficacy of melatonin for the alleviation of jet lag has been tested in several randomised placebo-controlled and uncontrolled studies. The Cochrane meta-analysis of randomised studies in airline passengers, airline staff or military personnel reported that melatonin, taken close to the target bedtime at the destination, decreased jet lag from flights crossing five or more time zones.

Melatonin is commonly used as a sedative to facilitate EEG recordings as reported in a large number of publications across the last 2 decades, including many randomised controlled trials.

Melatonin was an effective sedative that was generally superior to placebo and had similar efficacy to other sedatives but required less specialist support due to its inherently lower risks.

In published clinical studies, melatonin was well tolerated. No serious side effects are associated with melatonin administration in short or long-term studies. The most common AEs accompanying short-term (3 months or less) melatonin administration in clinical trials were headaches, dizziness, nausea, and drowsiness; however, no significant differences were observed between placebo and melatonin. Exogenous melatonin has no reported tolerance, dependence, or 'hangover effect' the following day.

Sustained release formulations of Melatonin do not provide an optimal source of melatonin for patients or disorders that respond better to a sharper pulse of melatonin, mimicking endogenous release. In practice sustained release formulations may be crushed to obtain more suitable kinetics, or in elderly or other patients who have difficulty swallowing. However, this does not allow for flexibility of doses and the consistency of the dose when taken in this manner has not been proven. A liquid formulation is more convenient for patients taking lower and higher doses or who have swallowing difficulties. Ceyesto is intended to provide an immediate release formulation of melatonin, with flexible dosing and an easily swallowed presentation.

Biopharmaceutics

No comparative bioavailability studies have been conducted by the Applicant and none are required for bibliographic applications.

Clinical Pharmacology

The clinical pharmacology of Melatonin is well-established. The clinical pharmacology of Ceyesto is suitable to provide melatonin levels for the specified populations and indications The pharmacology of Melatonin has no significant unfavourable aspects, particularly in the immediate release formulation.

It is evident from clinical studies that administration via an NG or other type of enteral tube is a precedent that is well accepted in the UK. The Applicant considers that on the balance of evidence that has been provided that the inclusion of advice in the Applicant's SmPC for an oral solution product is justified, improving patient safety, accuracy of dosing and removing the need for off-label or unlicensed practice.

Efficacy in Delayed sleep wake phase disorder (DSWPD)

Delayed sleep phase syndrome (DSPS) or Delayed Sleep Wake Phase Disorder (DSWPD) as defined by International classification of diseases (ICD-11), Diagnostic and statistical manual of mental disorders (DSM-V) and International classification of sleep disorders (ICSD-3) as a disorder in which a person's sleep is delayed by two hours or more beyond what is considered an acceptable or conventional bedtime. The delayed sleep then causes difficulty in being able to wake up at the desired time, but other aspects of sleep, such as arousals, quality of sleep, and sleep architecture are not significantly changed. Underlying the observed sleep disturbance is a misalignment of the circadian rhythm. In DSWPD the baseline DLMO is expected to be at least 2 hours delayed compared to environmental time, although there are no other direct disturbances of sleep or sleep architecture.

In the treatment of DSWPD melatonin treatment has 2 separate actions, the chronobiotic effect and the hypnotic effect. These two effects can be complementary or conflicting, depending upon the time of administration and the residual serum levels in the early morning hours. The primary intent of treatment of DSWPD with Ceyesto is to correct the misalignment of the circadian rhythm.. The clinical correlate is the sleep time in patients who choose their own bedtime or the sleep onset latency in those with a fixed bedtime. The secondary effect of Ceyesto in DSWPD is

enacted through support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect).

The 4 pivotal studies included 308 subjects with an age range of 6-65 years. Clinically and statistically significant improvements in SOT or SOL were reported in the melatonin treatment groups when compared to placebo [redacted] 25 minute improvement p=0.013; [redacted] 44 minute improvement p<0.001; [redacted] >30 min improvement, p<0.001; [redacted] a 44 minute improvement . p<0.01). Similar effects were seen for dim light melatonin onset (DLMO) a marker of circadian rhythmicity. No new safety signals were seen.

The critical appraisal of the literature and updated benefit risk analysis demonstrates the efficacy and safety of immediate release melatonin for treatment DSWPD in children, adolescents and young adults. Melatonin has been in well-established medicinal use for DSWPD within the EU for more than 10 years, with recognized efficacy and an acceptable level of safety. Based on the analysis of the peer-reviewed literature on the current knowledge on efficacy and safety of melatonin in DSWPD, the benefit/risk ratio of melatonin is considered to be positive.

Efficacy in Insomnia in Attention Deficit Hyperactivity Disorder (ADHD).

Attention deficit hyperactivity disorder (ADHD) by definition is characterized by attention disorders, impulsive behaviour and hyperactivity. Chronic insomnia is a common comorbidity of ADHD. It can be difficult to elicit from children the precise sleep complaint they experience. Difficulties in sleep onset are a robust measure of one subset of chronic insomnia and are a key component of the target of Ceyesto action in chronic insomnia. Approximately one third of medication-free children with ADHD experience chronic sleep-onset insomnia (SOI). This persistent disability to fall asleep at the desired time in the evening may exacerbate daytime mood, behavioural, and/or cognitive problems [redacted] Medication-free children with ADHD and SOI have a delayed evening increase in endogenous melatonin levels [redacted] and in children without ADHD this phase delay predicted a stronger sleep phase-normalizing effect of exogenous melatonin [redacted]. The intent of treatment with Ceyesto, as an immediate release melatonin formulation, is to target sleep processes within the first few hours after administration. The primary targets are correction of any misalignment of the circadian rhythm (chronobiotic effect) and support in initiating and maintaining sleep during the first few hours of the sleep cycle (hypnotic effect), effects which are similar across all sleep disorders and populations.

In the clinical literature, melatonin advanced sleep onset by 26.9 ± 47.8 minutes, compared to a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$) in a 4-week randomised, double-blind, placebo- controlled study conducted in 105 stimulant-free children of 6 to 12 years, with ADHD and chronic sleep onset insomnia [redacted]. In the melatonin group an advance of sleep onset >30 minutes was more common (48.8% of children) than in those who received melatonin (12.8%, $p = 0.001$). There was an increase in mean total time asleep of 19.8 ± 61.9 minutes with melatonin and a decrease of 13.6 ± 50.6 minutes with placebo ($p = 0.01$). As compared with placebo, the melatonin group showed a decrease in sleep latency ($p = 0.001$) and increase in sleep efficiency ($p = 0.01$). The mean score on sleep log item difficulty falling asleep decreased by 1.2 ± 1.3 points (35.3% of baseline) with melatonin and by 0.1 ± 0.8 points (4.3% of baseline) with placebo ($p < 0.0001$). There was no significant effect on behaviour, cognition, and quality of life.

From a critical appraisal of the review of the peer-reviewed literature which designated pivotal and supportive studies, it can be concluded that melatonin is a safe and effective treatment for insomnia in children and adolescents presenting with ADHD. Melatonin has demonstrated PD effects (DLMO) that can be anticipated to be of clinical value in improving insomnia and has shown positive impacts on parameters such as sleep onset latency and total sleep time. In addition, all studies recorded an improvement in alertness, fatigue, cognition and behaviour

compared to baseline. Melatonin was seen to be generally well tolerated with headaches and dizziness most commonly reported.

Based on the totality of evidence from the literature the Applicant has proposed that Ceyesto treatment should only be initiated in patients who have had an inadequate response to sleep hygiene measures, reflecting both non-responders and patients who relapsed following use of sleep hygiene.

In summary, based on the analysis of the peer-reviewed literature on the current knowledge on efficacy and safety of melatonin, the benefit/risk ratio of melatonin is considered to be positive. Therefore, Melatonin 1mg/ml oral solution can be recommended for the treatment of insomnia in children and adolescents (6-17 years) presenting with ADHD where sleep hygiene measures have been insufficient.

Efficacy in Short-term Sedation under Medical Supervision to Facilitate EEG

Melatonin is widely used in clinical practice in the UK and worldwide for sedation prior to diagnostic procedures such as EEG, MRI and ABR, particularly in younger patients or patients with NDD, who might otherwise be unable to keep still to allow satisfactory completion of the procedure, or would be subject to unnecessary anxiety.

The well-established use of melatonin as a sedative is most clearly documented when it is used to facilitate EEG recording.

Three studies were considered pivotal for the use of melatonin to facilitate EEG. In these 3 clinical studies across 636 chldren upto 18 years of age, melatonin was effective in ensuring that the sleep EEG could be completed (Melatonin 89.4% versus Triclofos 91.2%, [redacted] Melatonin 73.3% versus Midazolam 36.7% [redacted]). An augmentation dose of melatonin was needed in upto 25.4% of patients.

When all uses of melatonin as a sedative were considered, there were 17 randomised controlled studies in 2387 children, of whom 1335 received melatonin. Melatonin was administered orally or by nasogastric tube. Most studies found that melatonin had similar efficacy to the active comparator but required less specialist support due to its inherently lower risks. Safety was not evaluated in all the studies, There were no significant safety concerns in any studies. The most common AEs were nausea and vomiting.

In conclusion, melatonin has been in well-established medicinal use for paediatric sedation within the EU for more than 10 years with recognized efficacy and an acceptable level of safety and is firmly established in clinical practice across the NHS with National Guidelines and standards being in place. Therefore, the benefit/risk ratio of melatonin in this indication is considered to be positive.

Jet Lag

Jet lag is a common complaint of travellers who fly across a number of time zones. The symptoms of jet lag include reduced alertness, daytime fatigue, loss of appetite, reduced cognitive skills, and disruption of the sleep/wake cycle. In susceptible air travel passengers, jet lag may exacerbate affective illness and result in psychiatric morbidity. Dysregulation of circadian rhythms and melatonin secretion represent the common underlying factor in jet lag and other circadian disorders [redacted]

Typical symptoms of jet-lag are sleep disturbances and daytime tiredness and fatigue, though mild cognitive impairment, irritability, and gastrointestinal disturbances may also occur. Jet-lag is worse the more time-zones crossed and is typically worse following eastward travel as people generally find it harder to advance their circadian rhythm (body clock) than to delay it, as required following westward travel. Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet-lag by ~ 44%, and to shorten the duration of jet-lag [redacted]

[redacted]. In 2 studies of flights over 12 time zones melatonin effectively reduce the duration of jet-lag by ~ 33% [redacted] Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation of circadian rhythmicity / jet-lag, melatonin should not be taken before 20:00 hr or after 04:00 hr at destination.

There were no new safety concerns in these studies.

In conclusion, the benefit-risk can be considered positive for the jet lag indication proposed for this application.

Safety

Melatonin is a well-established active substance licensed in the EU for more than 15 years, with a recognized acceptable safety profile. This bibliographic application includes data from more than 10,000 patients treated with melatonin.

Adverse effects reported in clinical studies involving melatonin doses of 0.5 to 8 mg were typically mild, and often difficult to distinguish from symptoms of sleep disturbance. Transient drowsiness / sedation, headache, and dizziness / disorientation were reported; these same adverse effects, plus nausea, are those typically associated with use of melatonin in reviews of the safety of melatonin in humans. When used according to the label the risks of melatonin treatment are low, benign and self-limiting.

Conclusion

In conclusion, melatonin has been in well-established medicinal use within the EU for more than 10 years, with recognized efficacy and an acceptable level of safety. Based on the analysis of the peer-reviewed literature on the current knowledge on efficacy and safety of melatonin, the benefit/risk ratio of melatonin is considered to be positive. Therefore, Ceyesto 1 mg/ml Oral Solution is recommended for marketing authorisation for treatment of chronic insomnia in chlidren with ADHD, DSWPD in chldren and young adults, for the alleviation of subjective feelings of jet lag and for single use for short-term sedation under medical supervision to facilitate EEG.

7. REFERENCES

The referenced publications can be found in Module 5.4.

8. EXPERT STATEMENT

The expert statement can be found in the following pages.