2.5 Clinical Overview

Melatonin 1 mg/ml, oral solution

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This document has been prepared according to NTA, Vol. 2B-CTD and ICH M4E Efficacy guideline.

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2.5.1 PRODUCT DEVELOPMENT RATIONALE

The current Clinical Overview refers to a medicinal product containing **Melatonin** as active substance **in the form of oral solution and at the strength of 1 mg/ml.** The product is intended for oral use and will be indicated for **(i) the short-term treatment of jet lag in adults, (ii) sleep disorders in children and adolescents aged 6-17 years with attention-deficit/hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient and (iii) the management of shift-work disorder (SWD) in adults.** The formulation of oral solution offers an alternative formulation option for paediatric and adult patients who are not capable of shallowing tablets or capsules, thus, achieving an easier method of administration and improved treatment compliance. The relevant Marketing Authorisation Application is submitted under Article 10.a of Directive 2001/83/EC, as amended (Well-Established Use [WEU] Application). According to Article 10.a of Directive 2001/83/EC as amended, '*the Applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substance(s) of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety*'. Therefore, the test and trial results are replaced by appropriate scientific literature.

According to Annex I of Directive 2001/83/EC as amended, where it is stated that for the purpose of demonstrating that the constituent of a medicinal product has a well-established use, the following criteria should be taken into account:

a) the time over which a substance has been used with regular application in patients,

b) quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods,

c) the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

Therefore, a careful assessment of all these aspects has been performed by the Applicant, along with all the clinical data found in the published literature related to the pharmacology, pharmacokinetics (PKs), efficacy and safety of melatonin in general but also more specifically, for the oral route of administration.

Melatonin (*N*-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day-night cycle. Circulating levels of melatonin vary in a daily cycle, thereby regulating the circadian rhythms of several biological functions, including the sleep/wakefulness cycle. As its production is tightly linked to the light/dark cycle, melatonin's main hormonal systemic integrative action is to coordinate behavioural and physiological adaptations to the environmental geophysical day and season. The circadian signal is dependent on its daily production regularity, on the contrast between day and night concentrations, and on specially developed ways of action. During its daily secretory episode, melatonin coordinates the night adaptive physiology through immediate effects and primes the day

adaptive responses through prospective effects that will only appear at daytime, when melatonin is absent. Similarly, the annual history of the daily melatonin secretory episode duration primes the central nervous (CNS)/endocrine system to the seasons to come [redacted]

Melatonin secretion by the human pineal gland exhibits a pronounced age dependence. Secretion is minimal in newborns; it starts during the 3rd or 4th months of life (coincident with the consolidation of sleeping at night), increases rapidly at the age of 1-3 years and then declines slightly to a plateau that persists through early adulthood. Nocturnal melatonin secretion then starts a marked continuing decline in most people, with peak nocturnal levels in most 70-year-old subjects only a quarter or less of what they are in young adults. Melatonin is involved in numerous biological functions including synchronising circadian rhythms, including sleep-wake timing and blood pressure (BP) regulation, the stress response, aging, immunity and the control of seasonal rhythmicity including reproduction, fattening, moulting and hibernation. Its effects occur through activation of the melatonin receptors (MTs) or due to its role as an antioxidant [redacted]

Melatonin or *N*-[2-(5-methoxy-1H-indol-3-yl)ethyl]acetamide (IUPAC) is a member of the class of acetamides and tryptamines; more specifically, it is an acetamide in which one of the hydrogens attached to the nitrogen atom is replaced by a 2-(5-methoxy-1*H*-indol-3-yl)ethyl group. It has the molecular formula $C_{13}H_{16}N_2O_2$ and a molecular weight of 232.28 g/mol. In its pure form, melatonin appears as an off-white odouress crystalline powder and does not appear to exhibit polymorphism. It is very slightly soluble in water (0.01%) and diluted hydrochloric acid (0.08%) [redacted]

Melatonin has obtained the ATC Code N05CH01 for being a nervous system, psycholeptic, hypnotic and sedative, MT agonist for oral use *(WHOCC ATC/DDD)*.

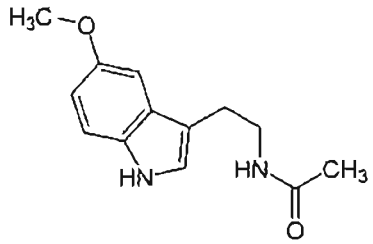

Figure 1. Chemical structure of Melatonin.

Melatonin was first identified by Dr. Aaron Lerner and his team at Yale University in the late 1950s, as the pineal substance responsible for bleaching in frog skin. It was found to be the 5-methoxy-*N*-acetylated derivative of serotonin or 5-hydroxytryptamin. For many years, it was considered to be only a hormone of the pineal gland. As soon as highly sensitive antibodies to indolealkylamines became available, melatonin was identified not only in pineal gland, but also in extrapineal tissues. These included the retina, Harderian gland, gut mucosa, cerebellum, airway epithelium, liver, kidney, adrenals, thymus, thyroid, pancreas, ovary, carotid body, placenta and endometrium. It has also been localised in non-neuroendocrine cells such as mast cells, natural killer (NK) cells, eosinophilic leukocytes, platelets and endothelial cells. This list

of cells indicates that melatonin has a unique position among the hormones of the diffuse neuroendocrine system. It is found in practically all organ systems. Functionally, melatonin-producing cells are part and parcel of the diffuse neuroendocrine system as a universal system of response, control and organism protection [redacted]

Melatonin is a well-studied human hormone, the pharmacological and toxicological profiles of which being well-known. The role of melatonin as a therapeutic agent is well-established within the European the Union (EU)/United Kingdom (UK), being tested in numerous large clinical trials through the past decades. Melatonin as immediate release (IR) formulations has been used both as medicinal product as well as food supplement since many decades in the management of various sleep disorders in adults and children, namely in adults for short-term treatment of jet lag, as well as other indicatons relative to its circadian effects, such as insomnia related to neurological disorders and shift work, as it resets disturbed circadian rhythms and promotes sleep [redacted] It is an approved medicine in the EU/UK for more than 10 years. A prolonged-release formulation containing 2 mg melatonin, Circadin®, has been registered in Europe since 2007 for the short-term treatment of primary insomnia characterised by poor quality of sleep, in patients aged ≥55 years [redacted]. IR products in solid formulations have been also authorised for sleep disorders in EU Member States and marketed since many years, with the first medicinal products being authorised back in early 00's, namely, Bio-Melatonin 3 mg Tablets [redacted] and Melatonin-LEK-AM 1 mg, 3 mg and 5 mg Tablets [redacted]. As far as the liquid dosage form of oral solution is concerned, it has to be mentioned that similar oral formulations are already registed in the UK, namely Melatonin Colonis 1 mg/ml oral solution [redacted] and Melatonin Consilient Health 1 mg/kg oral solution [redacted] Other melatonin oral solution products, e.g., Melatonin Unimedic Pharma 1 mg/ml oral solution [redacted] Melatonin Orifarm 1 mg/ml oral solution [redacted] and Voquily 1 mg/ml oral solution [redacted] are also authorised within EU. Most of the products have been approved based on bibliographic applications.

In addition, melatonin has been marketed as a food supplement in many countries and has been subject to regulatory opinion as such. Indeed, following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) of the European Food Safety Authority (EFSA) was asked to provide a scientific substantiation of a health claim in relation to melatonin and alleviation of subjective feelings of jet lag [redacted]. Due to the endogenous role of melatonin within the body, it has been extensively researched both *in vitro* and *in vivo* across various species including humans. Furthermore, the extended use of melatonin for more than 10 years to numerous patients and heterogeneous populations as well as the degree of scientific interest provide evidence of its well-known efficacy and safety profile. Additionally, the indications and recommended posology of the proposed product are similar to those investigated in the scientific literature and recommended for the proposed indications for EU/UK marketed IR products.

Overall, melatonin meets the criteria for classification as a well-established drug substance for which the Applicant is entitled to replace the results of non clinical studies and clinical trials by appropriate scientific literature and appropriate bridging documentation, since:

- Medicinal products containing melatonin have been used extensively in the EU/UK and worldwide, for several decades, with demonstrated efficacy and safety. Approved medicinal products for the treatment of jet lag disorder, insomnia in paediatric populations with ADHD as well as management of shift work disorder are already present in European markets since the early 00's and numerous food supplements are also marketed. Safety and efficacy of melatonin in the proposed indications have been also demonstrated in various clinical trials and can be considered as being well-established within the Community as well as worldwide. These are confirmed by extended data from the scientific literature and information of approved products' Summary of Product Characteristics (SmPCs).

- The use of melatonin formulations to numerous patients and heterogeneous populations, the degree of scientific interest, the well-known efficacy and safety profile of the active substance as well as the pharmaceutical form intended for authorisation prove the WEU.

- The indications and recommended posology of the currently applied melatonin oral solution product are similar to those investigated in the scientific literature claimed by already authorised products and recommended in clinical practice worldwide. Further clinical trials have involved the use of melatonin also for the treatment of other sleep disorders in adults and paediatric populations worldwide. The clinical aspects will be presented and discussed in detail within this Clinical Overview. The findings of the animal studies are also in agreement with the human results.

- In addition to the literature data, appropriate 'bridging data' are also included in the submission application in order to show the relevance of the literature data used to demonstrate the safety and efficacy of the actual product concerned. These will be discussed in detail within Section *'2.5.2 Overview of Biopharmaceutics'* of the current Clinical Overview. Additionally, the selected excipients are well-known for their use in the manufacture of pharmaceutical products and are not expected to modify the biopharmaceutics, *in vivo* performance, safety or efficacy profile of the active substance.

Considering the type of the present application as a WEU application according to Article 10.a of Directive 2001/83/EC as amended, concerning Melatonin 1 mg/ml oral solution, the Applicant is not required to provide new (own) clinical studies. Therefore, this Clinical Overview is based on extensive and comprehensive published scientific literature review and evaluation, related to the pharmacology, PKs, efficacy and safety of melatonin for the intended clinical indications in the target age population groups. The objective of this Clinical Overview is to critically evaluate the current information on the medicinal use of melatonin and to provide a critical assessment whether this drug has the required effects in the claimed indication, whether the recommended dosages per indication are suitable and whether the safety profile in terms of contraindications, precautions and adverse events (AEs) has been established. In this

respect, the Applicant has selected the most relevant studies/reviews which are used in the Clinical Overview to support this Application.

Further to the above, the qualitative formulation of the product contains, apart from the active substance, namely melatonin, also sorbitol 70%, propylene glycol (PPG), xanthan gum, citric acid anhydrous, paraben methyl sodium, orange IFF 3912, sodium citrate dihydrate, saccharin sodium and purified water, as excipients. As mentioned, the excipients included in the proposed formulation are commonly used ingredients for the formulation of oral solutions and are compliant with Pharmacopoeial requirements where applicable. Since the medicinal product under submission is also intended for paediatric use, namely in children and adolescents aged 6-17 years, elements of the *EMA Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) (EMA Guideline paediatric medicines, 2013)* was also taken into consideration. The excipients used exhibit a good safety profile and have been used extensively in other commercially available formulations, including other melatonin-containing oral solutions. All the amounts of excipients used are well below the reported toxic doses and acceptable daily intake amounts.

For the impurities present in the batches of the drug substance as well as those of the final product, please refer to the relevant parts of Module 3. Impurities in the active substance and in the finished product do not pose any special concern from a toxicological point of view and are in compliance with the European requirements. It can be recognised that the product under approval, as applied, has a comparable pharmaceutical quality as the similar products already authorised in Europe.

As a result, the excellent efficacy and safety profile of the product under approval has been confirmed in full agreement with the well-known biochemical properties of the active substance and the authorised products throughout the world that contain melatonin as active substance. For a detailed scientific bibliography to address the Clinical characteristics, please refer to Module 5.

2.5.1.1 SEARCH STRATEGY

In order to compile the Clinical Overview and demonstrate the well-established use of melatonin, among the public domain knowledge, a literature review was performed aiming to properly describe the relevant aspects regarding the pharmacology, PKs, efficacy and safety of the product in humans. This literature search has demonstrated that a broad experience exists on the clinical use of oral melatonin. A survey of the pharmacological properties of the drug is provided, as well as a detailed discussion on its efficacy and safety together with its overall place in current clinical practice. A detailed search was conducted within the biomedical databases; mainly in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) standard database, in IPCS INCHEM (www.inchem.org) database and also in the new locations of the former ToxNet (http://toxnet.nlm.nih.gov/) database. PubMed comprises more than 35 million citations for biomedical literature from MEDLINE, life science journals and online books. Citations may include links to full-text content from PubMed Central and publisher web sites. The former ToxNet tracks numerous databases within the US National Library of Medicine (NLM), related to toxicology, hazardous chemicals, environmental health and safety information (such as, Pubchem, ChemIDplus, LactMed, LiverTox). IPCS INCHEM is a

valuable tool for those concerned with chemical safety and the sound management of chemicals. Other literature of pharmacological and toxicological interest has been searched by using the current web engines, including sources such as EMA (European Medicines Agency), US-FDA (Food and Drug Administration), Classification by the monograph of IARC (monograph on the evaluation of carcinogenic risk to human), the US NTP (National Toxicology Programme), US OSHA (Occupational Safety and Health Administration), EFSA (European Food Safety Authority) DART (Developmental and Reproductive Database), Safety and Toxicity of Excipients for Paediatrics (STEP) database, World Health Organisation (WHO), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and Joint FAO/WHO Expert Committee on Food Additives (JECFA). The literature search included biomedical journals, medical literature and textbooks of recognised scientific relevance. Pre- and postmarketing studies were taken into consideration and special emphasis was put to include robust published literature.

At the first level, the review work included in the search the word *''melatonin''*. In a second round, more specific keywords such as *''pharmacology''*, *''pharmacokinetics''*, *''efficacy''* and *''safety''* were searched in relation to *''melatonin''*. Alternatively, reviews and meta-analyses were considered to identify other potentially relevant studies. The research was not narrowed in terms of dates. The search was restricted to the English language; however, papers written in another language, but with an abstract available in English were also considered. Both favourable and unfavourable documentation is being presented.

The search followed these steps:

- Performance of the literature search based on the above search terms and identification of the relevant studies from data sources like PubMed and others.
- A primary screen through titles, and then, abstracts for the search criteria above.
- Article selection based on their relevance to the topic.
- Review and interpretation of the findings.
- Based on findings, performance of additional and specific literature search aiming to complete the overall understanding, when necessary.

The general principles of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were also considered. PRISMA is a 27-item checklist primarily focusing on the reporting of reviews evaluating the effects of interventions and aims to help authors improve the reporting of original systematic reviews, updated systematic reviews or continually updated ("living") systematic reviews and systematic meta-analyses. Applicable items of the checklist were also applied in the current clinical overview.

The exploration reported here, which chronologically covers from the early 1960s till present, revealed that an extensive number of human studies exist defining the pharmacology, PKs, efficacy and safety profile of melatonin in humans. Although some of the old studies reported in publications mentioned in this report do not contain statements on compliance with Good Clinical Practice (GCP) regulations, in view of the amount of cumulated knowledge (as per February 2023, the term *'melatonin'* retrieved in the PubMed database over 30,900 results), the ultimately reported findings were considered valid to support the Clinical aspects of

melatonin. As these studies were published in peer-reviewed journals, there is no reason to assume that a repetition of these studies under current requirements would produce significantly different results.

2.5.1.2 INFORMATION ABOUT THE DISEASE

The International Classification of Sleep Disorders, Third Edition, defines Circadian Rhythm Sleep-Wake Disorders (CRSWDs) as persistent or recurrent patterns of sleep disturbance due primarily to one of the following: alterations of the circadian rhythm system or misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep. The circadian-related sleep disruption leads to insomnia, excessive daytime sleepiness or both. CRSWDs can be broadly divided into exogenous and endogenous subgroups (Table 1) [redacted]

Table 1. Categorisation of CRSWDs [redacted]

Disorder	*Brief Description*
Exogenous	
Jet lag disorder	Endogenous sleep-wake cycle is temporarily misaligned with the customary destination sleep-and-wake pattern following rapid travel across multiple time zones.
Shift work disorder	Symptoms of insomnia or excessive sleepiness that occur in association with work hours that overlap with the typical sleep period.
Endogenous	
Advanced sleep-wake phase disorder	Sleep-and-wake timing is advanced (i.e., earlier). usually by ≥2 h, than required or desired times.
Delayed sleep-wake phase disorder	Sleep-and-wake timing is delayed, usually by ≥2 h, relative to what is typically considered normal.
Irregular sleep-wake rhythm disorder	No clearly defined circadian rhythm; sleep-wake pattern varies from day to day.
Non–24-hr sleep-wake disorder	The intrinsic circadian pacemaker is not entrained to a 24-h light-dark cycle and the endogenous sleep-wake timing oscillates in and out of phase with the typical 24-h sleep-wake pattern.

Jet lag

Jet lag, also known as ''circadian desynchrony'', falls under the category of extrinsic CRSWDs. It is a sleep disorder in which there is a mismatch with the body's natural circadian rhythm and the external environment as a result of rapid travel across multiple time zones and is characterised by sleep disturbances, daytime fatigue, reduced performance, gastrointestinal (GI) problems, loss of mental efficiency, weakness, irritability and generalised malaise. Jet lag affects most air travelers crossing ≥5 times zones, the incidence and severity increasing with the number of time zones crossed [redacted] Retinal MTs have been found to be significantly relevant to the effects of melatonin on jet lag [redacted] This common problem affects all age groups but may have more pronounced effects on the elderly, whose recovery rate is more prolonged than in young adults. Overcoming the negative effects of jet lag requires adjusting the person's sleep phase into the new time zone of their destination, a concept referred to as ''sleep-phase shift''. In view of melatonin's clear chronobiotic effect, its role in regulating clock-controlled circadian rhythms has been firmly established. Thus, targeting the melatonin receptors for the purpose of shifting and stabilising

the circadian phase, represents a compelling pharmacologic approach [redacted]

Melatonin alleviates jet lag by its dual action as both a hypnotic and a chronobiotic [redacted]. It reduces nocturnal activity, position changes during naps, modulates the circadian rhythm of the sleep-wake cycle and improves sleep efficiency [redacted]. Therefore, melatonin has long been used as an over-the-counter (OTC) aid to assist with hastening sleep onset and treating symptoms of jet lag, with jet lag being the most common application. Also, following a request from the European Commission (EC), the NDA Panel of the EFSA concluded that a cause-and-effect relationship has been established between the consumption of melatonin and alleviation of subjective feelings of jet lag [redacted]. Many published guidelines of medical organisations, associations and institutions also promote the use of melatonin in the treatment of jet lag, namely the American Academy of Sleep Medicine (AASM), British Association for Psychopharmacology, Health Canada, Mayo Clinic, the International Federation of Sports Medicine and the US National Academy of Sciences [redacted], whereas treatment of jet-lag and other CRSWDs is included in the approved Product Information (PI) texts of several melatonin formulations already registered for this indication, including the UK approved similar liquid products.

Sleep disorders/Insomnia in ADHD

ADHD is commonly associated with disordered or disturbed sleep. The relationships of ADHD with sleep problems, psychiatric comorbidities and medications are complex and multidirectional. Evidence from published studies comparing sleep in individuals with ADHD with typically developing controls is mostly concordant for associations of ADHD with hypopnoea/apnoea and peripheral limb movements in sleep or nocturnal motricity in polysomnographic studies, increased sleep onset latency (SOL) and shorter sleep time in actigraphic studies, bedtime resistance, difficulty with morning awakenings, sleep onset difficulties, sleep-disordered breathing, night awakenings and daytime sleepiness in subjective studies. Psychostimulant medications, such as methylphenidate, which are widely regarded as first-line therapy for ADHD, are associated with disrupted or disturbed sleep (but also 'paradoxically' calm some patients with ADHD for sleep by alleviating their symptoms). Sleep problems are a prominent behavioural feature in childhood ADHD, with associations between the two ranging from 25% to 50% [redacted] to as high as 80% of children with ADHD manifesting these difficulties [redacted].

In the majority of cases, ADHD in children and adults is associated with a circadian rhythm disorder with delayed sleep onset. Treatment of insomnia should always start with sleep hygiene education and optimising the stimulant or non-stimulant treatment of ADHD. Careful titration of stimulants and psychoeducation around sleep optimisation can improve the quality of sleep, possibly due to improved daytime structure, the maintenance of regular physical activity and improved mood [redacted]. Also, published guidelines of medical organisations, associations and institutions have stated the probable

usefulness of melatonin for the treatment of sleep disturbances in ADHD. The Updated European Consensus Statement on the diagnosis and treatment of adult ADHD (2019) mentions that in children with ADHD and chronic insomnia, melatonin has been shown to advance the sleep onset and increase sleep duration [redacted]. The Canadian Pediatric Society (2012) mentions that melatonin treatment for certain sleep problems in children and adolescents can be useful in special populations. AEs due to melatonin use and pharmacological therapy for sleep problems appear to be mild and self-limited and should be considered only after a trial of sleep hygiene intervention [redacted] Moreover, in EU/UK, the use melatonin to treat sleep disorders in children and adolescents with ADHD is already approved in registered liquid melatonin products; before that, the use of unlicensed (''off-label'') melatonin products was widely practiced in the clinical setting.

Shift work disorder

Shift work comprises work schedules that extend beyond the typical ''nine-to-five'' workday, wherein schedules often comprise early work start, compressed work weeks with 12-h shifts and night work. According to American and European surveys, between 15 and 30% of adult workers are engaged in some type of shift work, with 19% of the European population reportedly working ≥2 h between 22:00 and 05:00. SWD is characterised by excessive sleepiness and/or sleep disruption for ≥1 month in relation with the atypical work schedule. Individual tolerance to shift work remains a complex problem that is affected by the number of consecutive work hours and shifts, the rest periods and the predictability of work schedules. Sleepiness usually occurs during night shifts and is maximal at the end of the night [redacted] The findings of a recent meta-analysis illustrated that night-shift work was associated with a decrease in urinary 6-sulfatoxymelatonin (a melatonin metabolite), while no significant association was observed between night-shift work and the change of blood or saliva melatonin level. Thus, night-shift work is associated with suppression of melatonin production, especially among fixed night-shift workers [redacted]. Several studies have indicated that both melatonin production and sleep patterns are altered in shift workers. It was found that nocturnal melatonin was out of phase with sleep initiation in 8 of 9 permanent shift workers. Similarly, another study noted a shift in melatonin rhythm in permanent night-shift workers. An alteration of the melatonin profile was seen in some shift workers, while in others, it was found to be indistinguishable from those seen in day workers [redacted]

Studies have associated non-standard shift work schedules and poor health outcomes, including increased risks of diabetes mellitus, dyslipidaemia, hypertension, heart disease, peptic ulcer disease and depression in shift workers. Moreover, non-standard shift work has been associated with a variety of negative health outcomes and urologic complications, especially with concurrent SWD. Further research into both pharmacologic and non-pharmacologic therapies for SWD is needed to establish more definitive guidelines in the treatment of SWD in order to increase productivity, minimise workplace accidents and improve quality of life for shift workers. Research on non-pharmacologic strategies for improving sleep quality in shift workers has focused mainly on behavioural therapy and sleep hygiene. Additionally, timed light exposure has been proposed as a method of shifting circadian phase in nighttime shift workers. Stimulants such as modafinil, caffeine and to a lesser extent methamphetamine have been suggested as pharmacologic agents for those with SWD to combat sleepiness and improve

psychomotor performance during night shifts. The use of sedative hypnotics for insomnia in shift workers is risky and potentially contraindicated in hazardous working environments, depending on the PKs of the drug. Although receiving melatonin or melatonin agonists prior to daytime sleep may help insomnia in night-shift workers, the recommended effective dosage and timing of melatonin administration remain variable [redacted]

Nevertheless, published guidelines of medical organisations, associations and institutions have stated the potential usefulness of melatonin for the management of SWD in adults. The AASM published in 2007 a guideline for the Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders stating that melatonin use prior to daytime sleep is indicated to promote daytime sleep among night shift workers. It further added that compared to placebo, melatonin administration prior to daytime sleep after night work shift improved daytime sleep quality and duration and caused a shift in circadian phase in some but not in all subjects, however failed to enhance alertness at night. Melatonin doses in these studies ranged from 0.5 to 10 mg and from these data, effectiveness did not appear to correlate with dosage strength or form [redacted] In addition to this guideline, the British Association for Psychopharmacology published an updated consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders [redacted] stating that there have been several reports on the use of melatonin in shift workers with beneficial results.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

As already mentioned, **this is an application according to Directive 2001/83/EC as amended, Article 10.a (so called WEU application), for melatonin oral solution at the strength of 1 mg/ml**, for (i) the short-term treatment of jet lag in adults, (ii) sleep disorders in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient and (iii) the management of SWD in adults. According to the EU legislation, for a WEU application, there is not a requirement to submit proprietary PK or clinical studies if the criteria set out in Annex I of Directive 2001/83/EC, as amended, are met. The pharmaceutical form of the current formulation is actually a liquid oral solution, containing the same active substance (i.e., melatonin) at the same strength (1 mg/ml) and intended for the use via the same route of administration as other currently authorised products in the EU/UK that are used in clinical practice; also, several studies have utilised IR liquid and solid formulations of melatonin and are published since decades. The indications and posology scheme are the same as those recommended and used in the clinical studies quoted in the scientific literature (utilising oral melatonin, IR formulations) and reflected in the SmPCs of the products approved in the EU/UK markets and worldwide. A detailed evaluation of clinical efficacy and safety data is presented in Sections 2.5.3 and 2.5.4 of this Clinical Overview.

Therefore, as basis for getting a marketing authorisation under Article 10.a of Directive 2001/83/EC as amended, no new clinical data or dedicated bioequivalence (BE)/PK studies are submitted. One should also have in mind that the product under submission is **not a generic** claiming essential similarity to a specific/dedicated reference product, **but a stand-alone application for an IR melatonin-containing oral solution formulation.** Thus, the WEU application should include the best possible 'bridge' between the product applied for and the published data, in order to make the judgement on whether the products included in the clinical studies in the submitted literature and the products already authorised and marketed in EU countries can be seen as similar to the product applied for. Therefore, in addition to the literature data, appropriate 'bridging data' are also included in the submission application, in order to show the relevance of the literature used to demonstrate the safety and efficacy with regards to the actual product concerned. These data, presented below, consist of evaluating the composition and product physicochemical performance in basic *in vitro* tests as well as a robust scientific justification based on the current scientific knowledge as derived through a detailed literature search and review.

Despite the fact that, as mentioned above the product is not generic claiming essential similarity to a specific reference product but a stand-alone application WEU Application, an *in vitro*, ''biowaiver-like'' approach, utilising elements of the Biopharmaceutics Classification System (BCS) was used for scientific bridging and the respective *EMA Guideline on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98/ Rev.1 Corr**, 2010)*, as well as the *ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018) (EMA ICH M9, 2020)* principles were considered. In view of this, the biopharmaceutic and PK properties of melatonin have been well evaluated by the Applicant; in the following Sections, the main issues to be discussed are focusing on:

- the potential classification of melatonin as a Narrow Therapeutic Index (NTI) drug;

- the critical evaluation of current literature and scientific knowledge on the biopharmaceutic/PK properties of melatonin and its BCS Classification;
- the assessment of formulation composition and *in vitro* dissolution characteristics of the new product.

2.5.2.1 MELATONIN'S POTENTIAL CLASSIFICATION AS AN NTI DRUG

An important starting point for the efficacy, safety and similarity establishment of a melatonin-containing medicinal product is whether the active substance should be considered and treated as an NTI drug.

NTI index drugs are defined by the US-FDA as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening, possibly resulting in hospitalisation, disability or even death [redacted]

NTI drugs generally have the following characteristics:

- steep drug dose-response relationship within the usual dose range or narrow span between effective drug concentrations and concentrations associated with serious toxicity;
- subject to therapeutic drug monitoring based on PK or pharmacodynamic (PD) measures to ensure safe and effective use of the drug;
- small within-subject variability.

In pharmacological terms, NTI drugs are defined as less than a 2-fold difference in median lethal dose (LD_{50}) and median effective dose (ED_{50}) or less than 2-fold difference in the minimum toxic and minimum effective concentration in the blood [redacted]

Melatonin is considered as being rather safe, as it is an endogenous substance that is well-tolerated even when administered at high doses. The most commonly reported adverse reactions of short-term melatonin use are nausea, headache, dizziness and drowsiness. In clinical studies, melatonin at usual doses of up to 10 mg daily appeared to be well-tolerated in patients [redacted] This result did not change by dose, the presence or absence of a sleep disorder, type of sleep disorder, duration of treatment, gender, age, formulation of melatonin, use of concurrent medication, study design, quality score and allocation concealment score [redacted] Melatonin doses of less than 8 mg have reportedly caused heavy head, headache and transient depression. Most clinical trials have shown that overall AEs of melatonin are insignificant and generally similar to those found with placebo [redacted] No hangover effects have been observed with melatonin when administered at reasonable concentrations, partially as a consequence of its short half-life ($t_{½}$). However, high doses (240-1,000 mg/day) administered in a small number of subjects were associated with hormonal changes that were inconsistent among the different reports. A meta-analysis of 10 controlled trials (over 200 subjects) in which melatonin used for ≤3 months showed only scarce reports of AEs [redacted]

In any case, the SmPCs of the approved melatonin products include posologies of up to 6 mg daily as being well-tolerated and there is generally no need to monitor blood levels. In published clinical trials, even higher daily doses have been administered being also proven safe. In these doses, no severe AEs have been observed in clinical or postmarketing surveillance studies. Based on the above sum of evidence, it can be concluded that **there is no scientific evidence to consider melatonin as an NTI drug.**

Overall, there is no scientific reason to classify melatonin as a ''Narrow Therapeutic Range Drug'', which would exclude it from bridging by applying ''*in vitro* approaches'' according to the US-FDA and EMA scientific guidelines.

2.5.2.2 BIOAVAILABILITY, BIOEQUIVALENCE AND BIOPHARMACEUTIC CONSIDERATIONS

According to Article 10.a of Directive 2001/83/EC as amended, the Applicant shall not be required to provide the results of pre-clinical tests or clinical trials (including bioavailability or BE studies), if he can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. Therefore, this application should be supported by published literature rather than proprietary studies carried out with the medicinal product under discussion, since, indeed, melatonin oral forms have a history of wide clinical use for the claimed clinical conditions in the EU/UK and worldwide for many decades and, definitely, far beyond the required 10 years of use. However, evidence has to be provided that the suitability of bibliographic data to demonstrate eligibility of WEU, through appropriate ''bridging'' with the products administered in the published clinical trials and/or the products authorised in EU/UK and used in clinical practice. This ''bridging'' exercise is, most and above all, based on a biopharmaceutic and PK thorough evaluation.

2.5.2.2.1 Bioavailability and bioequivalence issues

Despite the fact that, as mentioned above, the product is not generic claiming essential similarity to a specific reference product but a stand-alone application for a new melatonin oral solution formulation, the *EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, 2010)* has been consulted, in order to provide adequate evidence of similarity of the products under review to other currently authorised medicinal products or products used in the clinical studies presented in the current Clinical Overview, supporting the safety and efficacy of orally administered melatonin. Moreover, in order to understand the type and extent of ''bridging data'' and bibliographic documentation needed to support the present 'WEU-Application', the processes of melatonin absorption and factors that may have a critical impact on its bioavailability were carefully analysed.

2.5.2.2.2 Solubility, permeability and BCS attributes

Solubility

Melatonin appears as an off-white odouress crystalline powder that does not seem to exhibit polymorphism. It is a rather borderline solubility substance [redacted] with its water solubility being 0.01% or else 0.01 mg/ml [redacted] In

simulated gastric (pH 1.4) and intestinal fluid (pH 7.4), solubility was also low almost 3 mM [redacted]. Other authors, however, state a higher aqueous solubility for melatonin in room temperature at 0.4344 mg/ml [redacted]. The solubility of melatonin is not pH-independent in the pH values found in the human GI tract ranging from 1.2 to 7.8 [redacted] This finding is in accordance with its physicochemical properties indicating that it is non-ionasable [redacted] Further studies have demonstrated that the solubility of melatonin is independent from dose (in a range of 5-20 mg) and from taurocholate concentration (0.63, 1.25, 2.50 mmol). In order to increase its solubility, the addition of PPG [redacted] or surfactants [redacted] in an aqueous solution has been proposed.

According to the elements of the BCS [redacted] a substance may be classified as highly soluble if its dose-solubility ratio (D/S) is less than 250 ml over a defined pH range. The "dose" in this ratio was consistently defined as the highest dosage strength; however, the current EMA definition of "dose" for compliance to the solubility criteria pertains to the highest single dose administered as per the SmPC [redacted]
In the case of **oral IR melatonin formulations, the standard dose is 1-6 mg of melatonin daily.** Therefore, in the case of melatonin, it may be calculated that, even with a solubility of 0.01 mg/ml, for 6 mg (i.e., the highest recommended dose for the proposed uses of melatonin), the D/S is 60 ml (<250 ml). Although these calculations are not based on a formal solubility study as per the EMA Guideline requirements, they may be adequate to assume that the ratio is less than 250 ml, which means that the substance can be classified as highly soluble. Further to the above, according to Ullmann's calculations [redacted], although melatonin is slightly soluble in water, the dose number for a melatonin 5-mg capsule formulation is <1, which classifies it as highly soluble active substance. The reason is that considering a volume of 250 ml of water and a very low therapeutic dose, this substance is highly soluble as per Amidon's concept. In addition, during the evaluation of the data regarding Circadin® 2 mg prolonged-release tablets, despite its bordedline aqueous solubility, melatonin is classified as highly soluble in accordance with the BCS due to the low tablet strength [redacted]

Permeability

Regarding the permeability of melatonin, it has been found relatively high with a permeability coefficient in water Kp = 7.20 ± 1.43×10^{-4} [redacted] considered melatonin as being a highly permeable drug. Further literature data also support that the permeability of melatonin is high (Table 2).

Table 2. Reported permeability values of melatonin.

Reference	Melatonin dose	P_{app} A–B (cm/s)	P_{app} B–A (cm/s)	Efflux ratio (P_{app} B–A/P_{app} A–B)
[redacted]	6.5 µM	12.5 × 10^{-6}	-	-
	5 µM	~ 11.0 × 10^{-6}	-	-
	5 µM	11.56 ± 2.00×10^{-6}	11.58 ± 1.01×10^{-6}	1.0

Usually, molecules with permeability >10 nm/s in the Caco-2 system (1×10^{-6} cm/s) are classified as highly permeable and have intestinal absorption >90 % [redacted]

[redacted]. Other authors suggest a cut-off value of 100 nm/s (or else 10×10^{-6} cm/s)[redacted]. It is reported that the overall ranking of compounds with P_{app} $<1\times10^{-6}$ cm/sec, between 1-10 $\times10^{-6}$ cm/s and $>10\times10^{-6}$ cm/s can be classified as poorly (0-20%), moderately (20-70%) and well (70-100%) absorbed compounds, respectively[redacted] According to Table 2 and the data by [redacted] all reported values from literature are $>10\times10^{-6}$ cm/sec for melatonin indicating that the proposed product has high permeability and therefore, all IR dosage forms would be expected to act in a similar manner.

Melatonin is completely absorbed when administered orally, although its absolute bioavailability low due to a first-pass effect [redacted]

BCS Classification

The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). It categorises drug substances into one of 4 BCS classes as follows: *Class I:* high solubility, high permeability; *Class II:* low solubility, high permeability; *Class III:* high solubility, low permeability; and *Class IV:* low solubility, low permeability[redacted] *EMA ICH M9 Guideline BCS-based biowaivers, 2020).*

Having a rather borderline solubility and a high permeability, melatonin would be classified as BCS Class II drug [redacted]. However, as also reported above, it is classified as highly soluble in accordance with the BCS criteria due to the low doses clinically administered. Therefore, taking the scientific literature data into consideration, melatonin is considered and has been formally characterised as as both BCS and Biopharmaceutical Drug Disposition and Classification System (BDDCS) Class I drug [redacted] This categorisation has been also accepted within previous WEU applications of other melatonin-containing oral IR tablet formulations [redacted] as well as oral solutions [redacted] within the EU territory. Hence, no further solubility or permeability data/experiments are needed to confirm the BCS Class of melatonin.

PK evaluation

Further to the above, in order to elucidate and critically discuss the whole PK profile of melatonin and be able to bridge the product with the literature data, the Applicant has performed a thorough search in the scientific literature through which a wide variety of PK studies administering various doses of melatonin in various formulations and dosing conditions was identified. These studies and a further analysis of their PK results are presented (tabulated) in detail in Section *'2.5.3.1.1 Absorption and bioavailability'* of the current Clinical Overview. Different oral dosage forms of melatonin have been used in the cited literature articles and clinical trials; no differences are expected between the formulation under submission and the formulations used in the literature articles or the already EU/UK-authorised ones; the majority of the trials have been conducted with IR solid forms, while some limited data also exist with liquid oral formulations or modified-release products.

Here, it has to be mentioned that **melatonin also exhibits linear PKs.** Indeed, the data from the published studies by [redacted] suggest that **melatonin has linear kinetics over the range of 1-10 mg** (based on proposed methodology to assess linearity as in *EMA 2010 Guideline on the Investigation of Bioequivalence*) (Table 3). In particular, there is a trend for a more than proportional increase by increasing the dose; however, it does not exceed the threshold of non-proportionality between the usual therapeutic range of 1-10 mg. This finding is consistent with the SmPC of the centrally approved product, Circadin® 2 mg, stating that kinetics is linear over the range 2-8 mg *(SmPC Circadin).*

Table 3. Assessment of the PK dose-proportionality of melatonin.

[redacted]				
Dose (mg)	**AUC (ng×min/ml)**	**Dose-normalised AUC (ng×min/ml × mg)**	**Ratio**	**Linear**
4	530.57	132.64	N/A	N/A
2	237.77	118.89	89.63%	Yes
[redacted]				
Dose (mg)	**AUC (pg×min/ml)**	**Dose-normalised AUC (pg×h/ml × mg)**	**Ratio**	**Linear**
10	21,000.4	2,100.04	N/A	N/A
1	1,599	1599.00	76.14%	Yes
0.3	459.9	1533.00	73.00%	No
Abbreviations: AUC, area under the concentration-time curve.				

The linear PKs of melatonin has been also demonstrated for the oral dose range of 10-80 mg by [redacted]. Later, [redacted] showed linear PKs between 0.4 mg and 4 mg following administration of two different oral surge-sustained release (SR) doses in older adults. These data suggest, also, that **a saturable first-pass hepatic metabolism may be responsible for the apparent dose-dependent oral bioavailability in higher doses.**

The existence of an extensive first pass effect for melatonin has been also proposed by [redacted] their study found a markedly increased area under the concentration-time curve (AUC) for the ratio of 6-sulphatoxymelatonin to melatonin in plasma after oral as compared with intravenous (IV) administration (13±13 vs 1±1), which can be explained only if one assumes that there was considerable first-pass hepatic extraction after oral administration, giving rise to the conversion of melatonin to 6-sulphatoxymelatonin and thereby decreasing the bioavailability of melatonin. Obviously, the trend towards a more than proportional increase in the AUC, by increasing the dose, can be explained by the saturation of the first-pass metabolism. As it will be discussed in the corresponding subsection of the Pharmacokinetics, melatonin is mainly metabolised by the CYP1A2. For this isoenzyme, metabolism of most substrates can be described using the Michaelis-Menten equation, demonstrating saturation kinetics. **The saturable metabolism and subsequent nonlinearity is more obvious in high doses of melatonin.** For instance, some authors have commented that there is nonlinearity in the PKs of oral melatonin, with the calculated plasma AUC following a 2.5-mg dose being 0.0014 μg×h/ml, while that following an 80-mg dose was 0.465 μg×h/ml, i.e., a 332-fold difference in AUC corresponding to a 32-fold difference in dose [redacted] However, the administration of an 80-mg dose falls outside the scope of the proposed product. Indeed, as seen in the literature reviews of clinical trials [redacted] studies providing evidence of efficacy and

safety of melatonin in the treatment of jet lag involve mainly doses ranging from 0.5-6.0 mg, in the treatment of sleep disorders in children with ADHD involve mainly doses ranging from 1.0-6.0 mg and for SWD doses in the range of 1-10 mg; 3-6 mg are utilised in most cases and for all indications.

A detailed PK evaluation will be presented in the relevant Section 2.5.3.1.

Concluding, a generally low bioavailability of oral melatonin has been documented in a number of studies, fluctuating mainly from 3% to 36% [redacted]

Bioavailability presented a significant intra-individual variability, as typically anticipated for an endogenous substance. Moreover, the administration of different formulations also probably accounts for the great differences observed in bioavailability. As mentioned, it is generally agreed that the low bioavailability is caused by a considerable first-pass metabolism in the liver [redacted]. Overall, it can be observed that **variability of PK parameters is relevantly high.** Indeed, the PK parameters (maximum concentration [C_{max}] and AUC) displayed extensive variation within and between studies. The variations may obviously relate to interindividual differences in drug absorption, distribution, metabolism and elimination but may also be confounded by substantial variability in study designs/analytical methods. Other reasons accounting for these variations are probably, low absorption from the GI tract, an extensive first-pass metabolism in the liver or a combination of both. The variable bioavailability of oral melatonin is, therefore, not significantly related to differences in IR formulations but is rather due to the inherent properties and endogenous level fluctuations of the substance.

2.5.2.3 COMPOSITION OF THE PRODUCT, QUALITY ATTRIBUTES AND *IN VITRO* BRIDGING DATA

In order to fully investigate the product under submission, namely Melatonin 1 mg/ml oral solution, and achieve the best possible bridge between the product applied for and the published data, the Applicant has based their development on actual approved formulations and performed *in vitro* studies investigating critical quality attributes that may affect the *in vivo* performance of the formulation. An overview is presented below, whilst description and results can be found in Module 3.

2.5.2.3.1 Formulation composition, excipients investigation and *in vitro* dissolution

The medicinal product under review contains melatonin (1 mg/ml) in the form of (IR) oral solution. For the purpose of bridging the literature findings to the proposed formulation, the Applicant has performed a thorough investigation in order to identify the similar/appropriate products and substantiate the bridging to the literature data.

Given that some excipients may affect the *in vivo* behaviour of active substance, as a first step the Applicant has given emphasis in achieving close similarity, in terms of qualitative composition to other widely used and currently authorised melatonin oral solution formulations, containing the same amount of melatonin. In this context, the Applicant identified the qualitative compositions of similar products, mainly focusing on the UK

approved ones (Table 4). Evidently, the proposed product is in the same pharmaceutical form, intended for use via the same route of administration and contains melatonin in the same strength as other approved formulations. The products of Table 4 have been authorised under the WEU legal basis.

Table 4. Qualitative and quantitative (where available) composition of representative authorised melatonin IR **liquid formulations** within the EU/UK, as derived from the respective SmPCs (source: www.mhra.gov).

Product (MAH)	Indications	Posology	Excipients	Reference
[redacted]	Short-term treatment of jet lag in adults	Standard dose: 3 mg daily for a maximum of 5 days, which may be increased to 6 mg if the standard dose does not adequately alleviate symptoms. The dose that adequately alleviates symptoms should be taken for the shortest period. The first dose should be taken on arrival destination at the habitual bedtime.	PPG (E1520) (**150.50 mg/ml**) Sorbitol liquid (E420) (**140 mg/ml**) Sucralose (E955) Strawberry flavour (including PPG) Hydrochloric acid, concentrated (E507) Purified water	[redacted]
	Sleep onset insomnia in children and adolescents aged 6–17 years with ADHD where sleep hygiene measures have been inadequate.	Recommended starting dose: 1-2 mg (1.0-2.0 ml) 30-60 min before bedtime. The dose of melatonin can be increased by 1 mg (1.0 ml) every week until effect up to a maximum 5 mg (5 ml) per day, independent of age. The lowest effective dose that controls symptoms should be given.		
	Short-term treatment of jet lag in adult travellers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet lag symptoms on previous journeys. Travellers crossing 2-4 time zones can use it if need be.	Recommended dose: 1-5 mg 1 h before bedtime at destination.	Glycerol (E422) Sorbic acid Methyl parahydroxybenzoate (E218) (**1 mg/ml**) Sodium hydroxide (for pH adjustment) Purified water	
	Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.	1-2 ml (equivalent to 1-2 mg) 30-60 min before bedtime. The dose should be adjusted individually to a maximum of 5 ml (equivalent to 5 mg) daily regardless of age. The lowest effective dose should be sought.		
	As Melatonin Consilient oral solution	As Melatonin Consilient oral solution	Glycerol Sorbic acid Methyl parahydroxybenzoate	

Product (MAH)	Indications	Posology	Excipients	Reference
[redacted]			(E218) Sodium hydroxide (for pH adjustment) Purified water	[redacted]
	As Melatonin Consilient oral solution	As Melatonin Consilient oral solution	PPG (**150 mg/ml**) Sorbitol liquid (E420) (**140 mg/ml**) Sucralose (E955) Strawberry flavour Hydrochloric acid (for pH adjustment) Purified water	
	As Melatonin Consilient oral solution	As Melatonin Consilient oral solution	PPG (E1520) (**150 mg/ml**) Sorbitol liquid (non crystallising) (E420) (**140 mg/ml**) Sucralose (E955) Strawberry flavour (including PPG) Hydrochloric acid (for pH adjustment) Purified water	

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; MAH, Marketing Authorisation Holder; PPG, propylene glycol; UK, United Kingdom; WEU, Well-Established Use.

Excipients have been traditionally thought of as being inert, but some of them may have a significant impact on the ultimate pharmacological availability of a drug substance when added to a formulation. The magnitude of this effect will depend on the characteristics of the drug and on the quantity and properties of the excipients. According to the *EMA Guideline on the investigation of bioequivalence Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr** (EMA, 2010)*, excipients that might affect bioavailability, should be identified as well as their possible impact on drug solubility, GI motility, susceptibility of interactions with the drug substance (e.g., complexation), drug permeability and interaction with membrane transporters. Although the impact of excipients in IR dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS-class I) is considered rather unlikely it can not be completely excluded. This is why typically, excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product in BCS-based biowaiver approaches. In a similar way, since the Article 10.a legal basis is pursued in our case, the composition similarity as far as possible to the currently authorised products and those most commonly reported in the published clinical trials was targeted, as this consists of the main bridging strategy between the proposed formulation and the products in market with an established efficacy and safety clinical record.

In order to achieve similarity as far as possible to the already marketed formulations, the Applicant has referred to the composition of approved melatonin oral solutions and has performed pre-formulation studies in order to choose the excipients of the final formulation as well as *in vitro* studies investigating the performance of the formulation (please also refer to Module 3). The excipients tested are well-known excipients, which have been used in other already marketed products containing melatonin or generally in oral solutions and comply with relevant pharmacopoeial monographs. The final choice was also based on the process to be

used and the ease with which the target quality characteristics could be obtained. The formulation was developed in order to be close to the already marketed products, with close comparability in composition (especially in terms of potentially 'critical excipients') and specific attention to the applicability also in the paediatric population. The qualitative and quantitative composition of the formulation product under current submission is provided below (Table 5).

Table 5. Qualitative and quantitative (quantities per 1 ml) composition of Melatonin 1 mg/ml Oral solution.

From the qualitative compositions presented in Tables 4 and 5, qualitative similarity between the test product and authorised formulations is self-evident; most excipients contained in the proposed formulation product are qualitatively and in the case of sorbitol and PPG, also quantitatively similar to other approved products. Compatibility is acknowledged since these excipients were extensively used in other similar melatonin formulations. All aspects related to a) the potential impact of each and every excipient on the *in vivo* behaviour of the active substance melatonin and b) the potential safety of the excipients, are carefully and explicitly discussed, based on the current scientific knowledge and published literature. The results of this evaluation are briefly presented below. The safety of the used excipients is also extensively addressed in Section *'2.5.5.5 Safety of excipients'* of the present document.

The potential impact of excipients on the *in vivo* absorption/behaviour of melatonin is investigated and briefly presented below:

Citric acid anhydrous and Sodium citrate dihydrate

Citric acid is mainly used in formulations as either the anhydrous material or as its sodium salt to adjust the pH of solutions. Citric acid, although water soluble and anionic, is not expected to significantly affect the transport of melatonin, since melatonin is uncharged at physiological pH [redacted]

There are perhaps at least three mechanisms that citric acid or its salt can potentially impact drug absorption: dissolution [redacted] apparent drug permeability via pH-partition hypothesis [redacted] and modulation of membrane permeability [redacted] Citric acid can improve the dissolution profile of weakly basic drugs by lowering the pH of the surrounding environment within the GI tract. Specifically, lowering of the pH would deliver more protons to aid drug speciation to the more ionised state and thus, promote weak base solubilisation [redacted] However, changing the surrounding pH is not likely impactful for melatonin since it is already a highly soluble neutral compound.

While solubilisation generally is promoted by drug ionisation, permeation is generally promoted by the neutral species. For a weakly basic drug, the higher proportion of unionised drug within the gastrointestinal tract due to the pH-raising effect of sodium citrate may increase the apparent drug permeability via the pH partition hypothesis [redacted]. However, changing the surrounding pH again is not likely impactful for melatonin permeability since as reported melatonin is uncharged at physiological pH and is a BCS Class I drug already demonstrating high membrane permeability and rapid absorption. In this vein, [redacted] examined the ability of citric acid and tri-sodium citrate to increase the membrane permeability of oral protein formulations in Caco-2 monolayers and rat intestinal tissue. Findings showed that citric acid's ability to significantly enhance permeation *in vitro* and *ex vivo* via calcium chelation is very low. Calcium ions are required to form tight junctions. Citrate has multivalent-cation sequestration capacity that depends on the pH conditions of the surrounding environment. Formulations containing citric acid, which lower the pH, primarily dissociated into a non-dominant chelating species. Thus, this approach was not a potent chelator of calcium ions; tight junctions remained intact and did not cause any changes in absorption [redacted]

Overall, following a thorough bibliographic search in the public domain, no reports on citric acid having any effect on oral absorption and/or bioavailability of highly soluble/highly permeable drugs were identified. Since the current formulation is an oral solution in which melatonin is already dissolved at the time of administration, any potential impact of excipients on the solubility of the active substance is negligible. Melatonin also shows a high membrane permeability with rapid absorption rate, which suggests the absence of any influence on its *in vivo* bioavailability by citric acid or its sodium salt.

Orange IFF 3912

Based on information from the open literature, no specific data are available indicating any probability of the flavoring agent to disrupt the GI transit time, motility or drug absorption and permeability of melatonin in any way, when orally administered at doses regularly employed

in pharmaceutical dosage forms [redacted] Hence, no alterations of the rate of melatonin absorption and systemic bioavailability are expected.

Paraben methyl sodium

Preservatives like methyl paraben and propyl paraben, are not likely to have any effect on membrane permeability or absorption potential of melatonin. An extensive literature research performed revealed the absence of reports suggesting that parabens may influence in any way the bioavailability of either BCS Class I or III drugs. No reports exist also suggesting potential effects of parabens on the *in vivo* solubility of other drugs, GI transit time and gut motility as well as effects on membrane protein transporters. It can be, therefore, suggested that methyl paraben is not considered a critical excipient for drug absorption, which is further supported by the publicly available evidence in the scientific literature.

In the proposed melatonin formulation, methyl paraben is included in a very small amount and is, thus, considered practically inactive *in vivo*. No effect from the inclusion of methyl paraben on the *in vivo* performance of the proposed melatonin oral solution is expected, and there is no reason whatsoever to suppose that the current formulation will deviate in any way from the safety and efficacy record of the already authorised melatonin formulations. Of note, methyl paraben is also present in other authorised melatonin oral solutions [redacted] therefore, no impact on the *in vivo* behaviour of melatonin is expected similarly to the other already marketed melatonin oral solution products, having been approved based on successful bridging to IR melatonin formulations within scientific literature.

Propylene glycol (PPG)

PPG has been shown to affect brush border enzyme activities and nutrient uptake in the small intestine, as a result it has been proposed that intestinal absorption of drugs could be affected by the solvent. In a study it was reported that 0.5% PPG had no significant effects on transport of digoxin (BCS Class III) across an inverted rat gut sac *in vitro*. In another study, it was shown that a 2-g oral dose of the excipient did not significantly affect antipyrine (BCS Class I) or ampicillin (BCS Class III) bioavailability or gastric emptying time or small intestinal transit time in dogs [redacted]. Therefore, no AE is anticipated in the absorption of melatonin even following administration of the maximum dosage which equivalents to 900 mg PPG.

The effect of PPG on permeability of various compounds has been also investigated in Caco-2, where the tested concentration was 1.5%. It has been shown that PPG does not affect permeability, even of low permeable compounds [redacted]. The PPG content of the test formulation is, therefore, not expected to raise any concern regarding active substance absorption and permeability.

Taking into considaration that melatonin is a highly soluble substance (BCS class I drug substance) and the proposed formulation is an oral solution containing PPG in amounts (150 mg/ml) similar to other marketed melatonin oral solutions [redacted]

[redacted] no significant impact on this excipient on the biopharmaceutic properties and *in vivo* behaviour of melatonin is anticipated.

Saccharin sodium

Saccharin sodium is a strong organic acid almost completely ionised at physiological pH. It has nearly complete absorption from the gut (about 3% is recovered in the faeces in humans after normal and high doses) and is rapidly eliminated unchanged in the urine [redacted] Studies has shown that saccharin may disrupt intestinal epithelial cells barrier function *in vitro*, increase paracellular permeability and decrease transepithelial electric resistance (TEER) via a non-cytotoxic mechanism [redacted] However, contrary to the studies done at the cellular level, saccharin did not increase gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) in rats despite the fact that the concentrations of the sweeteners used in the study were 1,000-fold in excess of the amount used in diet soda [redacted]

Previous studies [redacted] also aimed to identify the effects of artificial sweeteners (AS) such as saccharin on the GI tract to determine whether they could be playing a role in GI symptoms in persons with irritable bowel syndrome (IBS). They found no studies on the effects of AS on GI symptoms in the general population, or more specifically in IBS patients. [redacted] hypothesised that AS have the potential to affect the GI system since AS can interact with sweet taste receptors in the GI tract. While AS, like nutritive sugars, interact with gut sweet taste receptors, *in vivo* research collectively supports that this interaction does not lead to clinically relevant changes in GI health. In a recent review, [redacted] reported that human gut exposure to AS consistently fails to replicate any of the effects on gastric motility, gut hormones or appetitive responses evoked by caloric sugars. Likewise, the majority of *in vivo* laboratory animal research showed no clinically meaningful changes in GI hormones associated with taste receptor activation by AS, including saccharin [redacted] Robust research demonstrates the safety of AS in both humans and animal models and led to the approval of these sweeteners as food additives by regulatory agencies. It should be noted that many studies reviewed by regulatory agencies around the world have particularly assessed the potential for effects on GI heath and found them to have no effect. This is based on numerous types of measures, including, for example, evaluation of hematologic and biochemical analyses, macroscopic and microscopic examination of GI tissues. The collective literature, therefore, clearly supports that human consumption of such AS is without AE on GI health and function [redacted]

In the proposed melatonin formulation, saccharin is included in a small amount, which is not expected to affect gastrointestinal motility or any of the absorption processes of the active substance and is thus considered practically inactive *in vivo*. No effect from the inclusion of saccharin sodium on the *in vivo* performance of the proposed melatonin oral solution is expected and there is no reason whatsoever to suppose that the current formulation will deviate in any way from the safety and efficacy record of the already authorised melatonin formulations.

Sorbitol

Sorbitol is well acknowledged as one of the excipients that might affect the GI transit. For this reason, regarding oral solution, the *EMA Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98/Rev. 1 Corr**) (EMA, 2010)* recommends: *"If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients may affect gastrointestinal transit (e.g., sorbitol, mannitol, etc.), [...], a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers....."*. Further recommendations in same Guideline Appendix III, section IV.2 on excipients state: *"As a general rule, for both BCS-Class I and III drug substances [...] Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product."*

The effect of sorbitol on drug bioavailability may vary among compounds of low and high intestinal permeability, with drugs of low permeability (BCS class III drugs) showing in some cases diminished bioavailability and drugs with high permeability (BCS class I drugs) being practically unaffected [redacted] It is generally considered that the osmotic effect may have a higher impact on the absorption of low permeability drugs. In general, the issue of "active" excipients is particularly relevant for BCS class III drugs because these compounds often exhibit site-dependent absorption properties and transit time through specific regions of the upper intestine may be critical for drug absorption [redacted] However, the effect of sorbitol is dose- and drug-dependent and not all BCS Class III drugs may be affected [redacted]. In this respect, for the two BCS Class III drugs, lamivudine and ranitidine the solution formulations showed diminished oral bioavailability in presence of sorbitol [redacted], whereas cimetidine and acyclovir (BCS class III), did not show any changes in pharmacokinetic profiles due to sorbitol [redacted] On the other hand, the effects on BCS Class I drugs are generally absent, with drugs such as theophylline and metoprolol, being basically unaffected by sorbitol, even in cases where very high amounts of sorbitol were used [redacted]

All of the above is also reflected in the EMA published Questions & Answers on Clinical Pharmacology and Pharmacokinetics. Based on the -then- available literature data, EMA had arbitrary set a theoretical limit of 1.25 g as a single dose 'threshold' for the sorbitol effect on drug bioavailability. In this Q&A dynamic list of questions, it is actually stated that the best estimate of a single dose threshold for the sorbitol effect on drug bioavailability is probably around 1 g, affecting all drug BCS classes, but mainly low permeability drug substances (BCS III and IV). It also needs to be recognised that sorbitol intolerance is largely described in the literature. This means that a dose effect relationship cannot be established universally due to individual susceptibility. However, more data has to be collected to determine the actual threshold by exploring sorbitol doses lower than 1 g [redacted]. With modeling and simulation approaches, it has been estimated that sorbitol levels of less than 400 mg had minor

effects on the PKs of the most sensitive drugs, indicating a provisional no-effect threshold dose [redacted]

In view of the above, it is evident that sorbitol is a 'critical excipient' that might significantly affect the performance of certain medicinal products. As melatonin is BCS class I and exhibits a rapid and almost complete absorption and the amount of sorbitol (140 mg/ml) used in the formulation is small, no concerns regarding its biopharmaceutic impact on the bioavailability of the proposed melatonin formulation are expected to be raised. Indeed, for the clinically administered doses (i.e., 840 mg, taking the maximum daily dose of 6 mg or else 6 ml of oral solution into consideration), the ingested sorbitol amount is below the ''threshold'' set by the EMA. Last but not least, sorbitol is also present in the other authorised melatonin oral solutions in the same amount; therefore, no impact on the *in vivo* behaviour of melatonin is expected similarly to the already marketed melatonin oral solution products [redacted], having been approved based on successful bridging to IR melatonin formulations within scientific literature.

Xantham gum

There are no indications in the published scientific literature that xanthan gum has any significant impact on either GI motility or permeability of the drug [redacted]

A recent study by [redacted] investigated the impact of two thickeners, modified maize starch and xanthan gam on dissolution rate and bioavailability of levetiracetam, a BCS Class I drug. New Zealand albino female rabbits were divided into control and test groups. Powdered levetiracetam tablets were mixed with water thickened with xanthan gum (n=9, 1.2%, 2.4%, 3.6%) at three thickness levels and administered to the rabbits by intragastric gavage. No significant difference in total amount of levetiracetam absorbed (AUC) was found between groups (P=0.215 and P=0.183 for $AUC_{0-\infty}$ and AUC_{last}, respectively). These results suggested that regardless of the thickness level, the administration of levetiracetam with xanthan gum does not affect the PK behaviour and thus, the bioavailability of the drug.

In the proposed melatonin formulation, xanthan gum is used in small amounts, which is not expected to affect any of the absorption processes of the active substance. Given the fact also that melatonin is a BCS Class I drug, no effect from the inclusion of this inert excipient on the *in vivo* performance of the proposed melatonin oral solution is expected.

Overall, the qualitative and quantitative similarity of composition with currently authorised products leads to the conclusion that no difference in *in vivo* behaviour of the under-submission product compared to the registered ones is anticipated. As mentioned, a thorough safety evaluation has been also performed for the contained excipients; no significant safety issues related to the excipients are anticipated even for the intended paediatric population as it is further analysed in Section 2.5.5.5.

The important quality characteristics of the active substance and finished product are well-defined and controlled, and the product is formulated, manufactured and controlled in a way

that is characteristic for this specific type of formulations. In this context, the submission dossier of Melatonin 1 mg/ml oral solution includes all necessary evidence (e.g., analytical, manufacturing, stability data etc.) clearly demonstrating the high quality of the product. The finished product specifications proposed for the test product are in accordance with European Pharmacopoeia and ICH guidelines. Thus, there are no outstanding quality issues which may have a negative impact on the benefit/risk balance. The detailed results of these tests are presented in the relevant sections in Module 3 of the current submission dossier.

An additional issue of discussion is the actual release of the drug from the pharmaceutical form. Indeed, in terms of PKs, the fact that the drug is already in a dissolved state, as the dosage form refers to an oral solution, has to be investigated in terms of potential effect on its PK behaviour and as a result, its therapeutic performance, in terms of efficacy and safety. This is also important, given the fact that the liquid formulation needs to be ''bridged'' not only to similar/regisnered liquid products but also to solid forms (solid IR forms were usually administered in published PK and clincial trials).

The Applicant performed *in vitro* dissolution studies in order to compare the release profile of marketed melatonin-containing solid medicinal products (tablets) vs the developed drug product formulation (oral solution) under current submission in which melatonin, the drug substance, is already dissolved. For these studies, three marketed products, namely [redacted] all at the strength of 3 mg/tablet, and three batches of Melatonin oral solution were tested under three pH conditions, i.e., 0.1N hydrochloric acid (HCl), phosphate buffer pH 4.5 and phosphate buffer pH 6.8. The measurements were performed by means of the in-house validated analytical dissolution method. The dissolution studies have been conducted according to the recommendations of the *EMA Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, EMA 2010)*. A summary of results of the *in vitro* dissolution studies is presented below; for detailed data please refer to Module 3.

Table 6. Dissolution profiles of the marketed products [redacted] and the batches of the test product Melatonin 1 mg/ml Oral Solution in 0.1N HCl, phosphate buffer pH 4.5 and phosphate buffer pH 6.8.

[redacted]

The comparison of the dissolution profiles of the marketed products (Melatonin tablets) vs the developed drug product (Melatonin 1 mg/ml oral solution) concluded to the abovementioned results. As more than 85% of the drug is dissolved within 15 min, dissolution profiles are accepted as similar without further mathematical evaluation. Those results show a complete release of the drug substance, melatonin, before 15 min under all conditions tested in all products, irrespective of their nature. Hence, the products could be considered comparable.

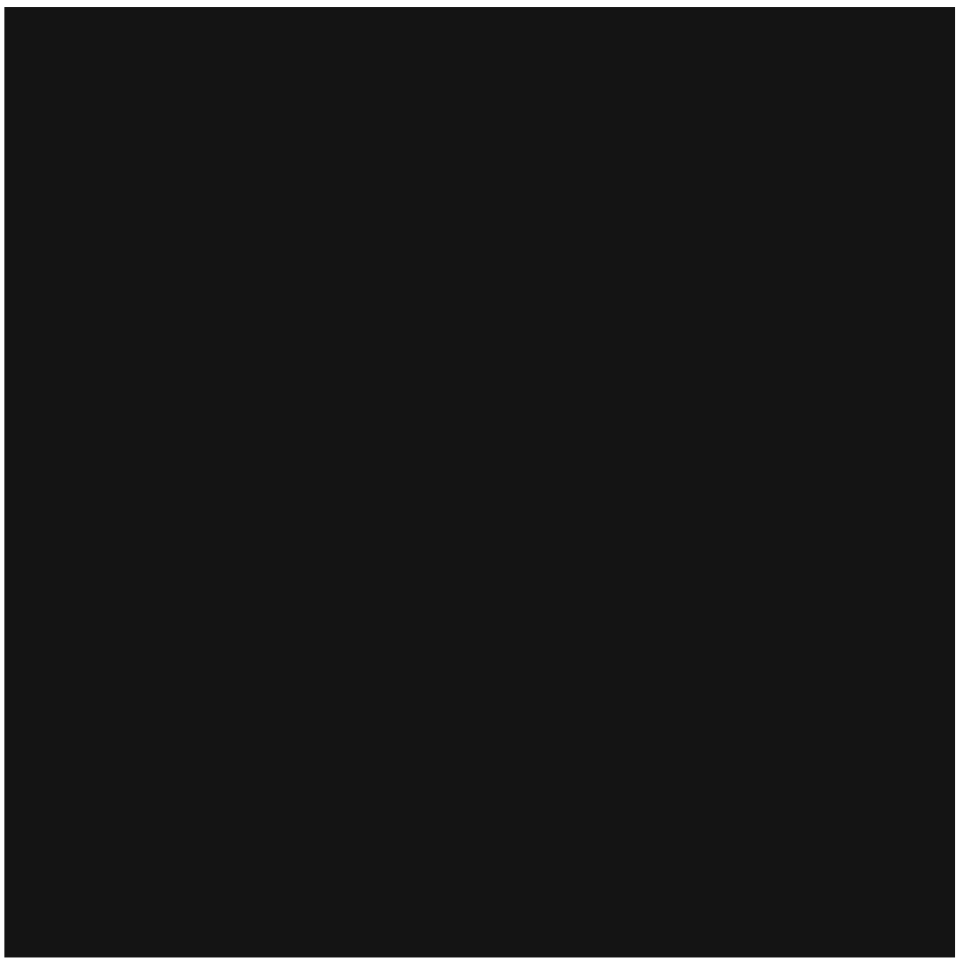

Figure 2. Graphs comparing the dissolution profiles of the test product Melatonin 1 mg/ml oral solution (Batch No.: with the three marketed products at the tested dissolution media, as recommended by the EMA Guideline.

In addition, in the Section of Pharmacokinetics (2.5.3.1) of the current Clinical Overview, the most relevant PK studies with IR formulations and with the intended dosing are presented, reviewed and thoroughly discussed. It has, however, to be mentioned that formulations administered in those PK studies are mostly melatonin-containing food supplements or nurse-prepared formulations, liquid and solid capsules or tablets and not branded EU-approved medicinal products. This means that the exact formulations administered cannot be retrieved in order to perform a proprietary *in vitro* comparison; this is also the case for the majority of clinical trials being conducted with administration of solid melatonin IR forms. Based, however, on the overall conclusions of these published data, it can be observed that the variability of PK parameters is rather high. This variability of oral melatonin is not related to the differing IR formulations but is due to the variability derived from the extensive first-pass metabolism of melatonin, meaning an inherent PK property of the active substance. Of note, it has been also indicated that the bioavailability of liquid forms is comparable to those of the IR solid forms. Once the current product has been successfully compared *in vitro* to both marketed liquid and solid formulations which have been supported by the same published scientific literature, one can ensure that the overall bridging also to the findings of published PK/clinical trials is self-evident.

2.5.2.4 CONCLUSIONS

Taking into consideration the overall scientific discussion as presented in above Sections, it may be concluded that, in view of the long-standing use of oral melatonin IR (solid and liquid) formulations in clinical practice, the proposed product is eligible to be submitted as a 'well-established use' application. No new PK, PD, efficacy and safety data are needed. Demonstration of pharmaceutical similarity, i.e., composition similarity with currently authorised oral IR solutions containing the same active substance as per EMA recommendations, as well as *in vitro* release similarity with marketed IR melatonin solid forms is applied for the building of the ''bridging data'' that are crucial for this type of application, naturally combined to robust literature data. It is summarised that:

- The application of Melatonin 1 mg/ml oral solution is submitted under Article 10.a of Directive 2001/83/EC as amended, namely, fulfilling the criteria of WEU application. This is a stand-alone application and the product is not considered generic where essential similarity vs a dedicated reference product has to be established, although, obviously, approved formulations have been used as a guidance for the development process. Therefore, there is no need to prove the efficacy and safety of the active substance, melatonin, through new own data since these are established through the clinical practice of melatonin for over 10 years as indicated by the appropriate literature data.
- No new non-clinical or clinical data need to be generated for such type of application; however, emphasis is given on quality data, providing robust evidence of ''similarity'' with the authorised formulations in critical excipients and quality attributes.
- The pharmaceutical form for this product containing melatonin is an oral solution, same as other approved products. As a principle, the Applicant tried not to deviate significantly from the composition of the authorised liquid formulations; therefore, the qualitative composition of the proposed product is very close to that of other authorised products. All the proposed excipients are well-known and are widely used in pharmaceutical preparations (oral solution), including melatonin-containing oral solutions, therefore incompatibility and interaction issues are not expected. Hence, no difference in *in vivo* behaviour of the product under submission compared to the registered ones in same form is anticipated. No significant differences in terms of qualitative composition are observed, especially this being important in the case of identified ''critical excipients''. The Applicant additionally performed *in vitro* dissolution studies in order to compare the release profile of marketed melatonin-containing IR solid medicinal products (tablets) vs the developed drug product formulation (oral solution) under current submission in which melatonin, the drug substance, is already dissolved. Similarity in release profile has been observed also in these cases, despite formulation differences.
- In the current submission, the Applicant has reviewed several literature references supporting the PKs, PDs, efficacy and safety results presented within this Clinical Overview. The whole PK data, which were thoroughly analysed and presented within the Overview, as well as the classification of melatonin as a BCS Class I substance and the similarity of the proposed formulation to the already approved ones, render that the justification of the product itself as appropriate for claiming an extrapolation of efficacy and safety from published data to the current product as acceptable. In view of the pharmaceutical similarity in terms of critical excipients between the product under review and the currently authorised formulations, no differences in the *in vivo* performance of the product are expected from a biopharmaceutical point of view.
- In order to elucidate and critically discuss the whole PK profile of melatonin, the Applicant has also performed a thorough search in the scientific literature through which a wide variety of PK studies administering various doses of melatonin in various formulations and dosing conditions was identified. Melatonin is rapidly and almost completely absorbed. It also exhibits linear PKs over the therapeutic range. It has been demonstrated that there is a trend for a more than proportional increase by increasing the dose; however, it does not exceed the threshold of non-proportionality between the

usual therapeutic range of 1-10 mg. However, as the proposed melatonin formulation is intended for short-term use at doses ranging from 3 to 6 mg, the administered doses are within the range of PK linearity.

- It has also to be mentioned that formulations administered in published PK/clinical studies are mostly melatonin-containing food supplements or nurse-prepared formulations, liquid and solid capsules or tablets and not branded EU-approved medicinal products. This means that the exact formulations administered cannot be retrieved in order to perform a proprietary *in vitro* comparison; this is also the case for the majority of clinical trials being conducted with administration of solid melatonin IR forms. Based, however, on the overall conclusions of published PK data, it can be observed that the variability of PK parameters is rather high. This variability of oral melatonin is not related to the differing IR formulations but is due to the variability derived from the extensive first-pass metabolism of melatonin, meaning an inherent PK property of the active substance. Of note, it has been also indicated that the bioavailability of liquid forms is comparable to those of the IR solid forms. Once the current product has been successfully compared *in vitro* to both marketed liquid and solid formulations which have been supported by the same published scientific literature, one can ensure that the overall bridging also to the findings of published PK/clinical trials is self-evident.
- A thorough safety evaluation has also been performed for the contained excipients; no significant safety issues related to the excipients are anticipated even for the intended paediatric population group (please refer to Section *'2.5.5.5 Safety of excipients'*). The similarity of composition compared to the authorised products, as well as the same claims in terms of clinical use and route of administration, additionaly ensure the suggestion that the new product is devoid of any local/systemic tolerability issues; no further safety studies are needed to be performed.
- The product under submission fulfilled all the criteria concerning the quality of oral solution formulations according to the EMA Guidelines, following the appropriate *in vitro* tests. The important quality characteristics of the active substance and finished product are well-defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic for this specific type of formulation. In this context, the submission dossier of Melatonin oral solution at the strength of 1 mg/ml included all necessary evidence (e.g., analytical data, manufacturing, etc.) which clearly demonstrated the product's high quality. The finished product specifications proposed for the test product are in accordance with European Pharmacopoeia and ICH guidelines. There are no outstanding quality issues which may have a negative impact on the benefit/risk balance. The detailed results of the tests are presented in the relevant reports which are included in Module 3 of the submission dossier.
- It is overall considered that the biowaiver-like approach may successfully bridge the new formulation product in terms of efficacy and safety to the already existing oral IR melatonin solid and liquid products in EU/UK markets/clinical practice and can further be safely extrapolated also to the ones administered in the clinical trials of the literature.

Last but not least, the risk of potential ''bioinequivalence'' is also considered, following the overall scientific evaluation performed. Situations could be envisaged resulting from a false

biowaiver decision, that is, declaring a test formulation bioequivalent to the reference formulation, whereas this test formulation would be declared bioinequivalent when subjected to an *in vivo* BE study. The test formulation may give rise to a lower or to a higher AUC and/or to a lower or to a higher C_{max} than the reference product. In the first instance, the test formulation has a lower AUC than that of the reference product and, thus, might be clinically less effective. This would have serious clinical consequence only in severe disorders that require increased dosages treatment, which is not the case for melatonin in the proposed indications. The second situation in which a false biowaiver decision would be clinically relevant is when the drug formulation is superbioavailable, that is, the test formulation has a higher AUC/C_{max} than the comparator(s). In this situation, the broad therapeutic index of melatonin would protect the patient from very serious side effects, as no serious side effects have been observed with this active substance, even at exceptionally high (acute) doses and serum levels, taking also into account the well-established proposed low dose to be administered for a short time.

Overall, from a biopharmaceutical point of view, the current formulation may be considered successfully 'bridged' with the melatonin oral solid and liquid formulations used in the EU/UK clinical practice and the published studies and no *in vivo*/BE/clinical data are necessary for bridging the current formulation with the literature data in the context of this WEU application. The quality and the *in vitro* proprietary data, as well as the critical evaluation and justification based on the current publicly available scientific knowledge, provide assurance of the efficacy and safety of the current product.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 PHARMACOKINETICS

The PK properties of melatonin are well-known. Oral IR melatonin is rapidly absorbed from the small intestine. The time-to-reach-C_{max} (T_{max}) is 15-90 min (mean: ~50 min). Oral bioavailability of melatonin is low, i.e., ~15 %. Increase in the C_{max} can be expected if melatonin dose is taken with food. Even it is not expected to affect the efficacy or safety, melatonin is not recommended to be taken concomitantly with food. Exogenous melatonin passes the blood-brain barrier (BBB) and distributed in all body fluids and tissues. Melatonin is mainly metabolised in the liver by the CYP1A2 with contribution from CYP1A1 and CYP2C19, yielding 6-hydroxymelatonin; the sulphate conjugate of the latter is a principal metabolite, but is inactive. Metabolism is very rapid, metabolite level rising within minutes. Metabolites are excreted in the urine. The elimination half-life ($t_{½\beta}$) is approximately 45 min. The kinetics of oral melatonin are linear over range 0.1-10 mg.

2.5.3.1.1 Absorption and bioavailability

Oral route of administration

A thorough critical reviewing of the available PK studies involving oral administration of melatonin formulations in humans has been performed. An overview of published PK studies utilising melatonin is presented in Table 7 below.

Table 7. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin formulations at low doses ranging from 0.1 to 100 mg to healthy volunteers.

Reference	Dose (mg)	Dosage form	Time of intake	Dosing condition	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	Cl/F (L/min)	F (%)
	2	Gelatine capsule	10:00	Fasted	2.80	15	32	222.72	-	-
				Fed	6.80	30	-	482.16	-	
	2	Corn oil preparation		Fasted	3.50	30		237.18		
				Fed	4.40	30	40	349.56		
	5	Tablet	Morning	Fasted	12.40	37.5	51.9	1179 [1]	-	-
	2	Sustained-release tablet	10:00	Fasted	0.43	96		151.62		
				Fed	0.48	156		144.30		
	2	Tablet	07:00-09:00	Fasted	2.18	52	61	237.77 [1]	-	14
	4				5.77	60	65	530.57 [1]	-	16
	0.5	-	-	-	-	-	47	-	-	33
	0.1	Capsule	11:45	-	0.05	135	-	12.79	-	-
	0.3				0.12	135	-	27.59	-	-
	1				0.40	135	-	95.94	-	-
	0.25	Oral solution (male)			0.24	23	36	14.16		
	0.25	Oral solution (female)			0.62	23	45	42.08		
	0.4	Oral (25% dose IR and 75% dose CR)			0.41	78	108	95.70	6.32	

Reference	Dose (mg)	Dosage form	Time of intake	Dosing condition	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	Cl/F (L/min)	F (%)
	4.0	Oral (25% dose IR and 75 % dose CR)			4.00	90	126	727.4	7.97	
	5	IR	10:00	-	2.18	-	-	372	-	-
	6	Tablet IR	08:30	-	4.48	60	106	-	3.08	-
	6	Tablet IR	09:00	Fasted	1.80	60	37	138(*)	132.50	-
	5	Capsule IR	-	-	4.82	30	38	256.89(*)	-	-
	10	Controlled release			3.82	45	48	507.91(*)		
					4.07	210	50	595.40(*)		
	0.5	Capsule	0.5 h before sleep	-	0.84	30	42	134.28	-	-
			4 h after bedtime		0.70	60	42	78.81	-	-
	5	Slow release			8.77	167	91	2.3×10^3	3.09	
	6	Tablet	09:00	Fasted (different age)	16.76	30	46	1,180	8.44	-
					16.44	53	52	1,240	9.88	-
	3	Capsule	09:30	-	0.68	60	68.4	99.78	-	-
	1	Capsule powder			0.80	60		90.5	-	-
		Soft-gelatine capsule	-	-	2.62	60	-	283.2		
	3	Capsule powder			2.40	40		269.1		
	2.5	Capsule	23:00	-	3.17	540	-	635.15	-	-
	3	-	09:30	-	3.56	20	-	-	-	-
	25	Capsule	09:30	Fed smoking	0.64	90		102.41		
				Fed non-smoking	1.86	90		294.00		
	100	Gelatine capsule	09:15		101.16	60	41			
	80	Gelatine capsule	11:00				48	27.87×10^3		
	3×80		11:00, 12:00, 13:00					31.30×10^3		
	0.3	Capsule	0.5 h before sleep	-	0.20	60	-	42.71	-	-
	5	Capsule			2.05	120	-	426.47	-	-
	0.3	Capsule	21:00	-	0.11	49.8	-	29.94	-	-
	0.3	Gelatine capsule	11:00	-	0.17	48	-	26.51	-	-
					0.26	45	-	35.75	-	-
	0.1	Capsule	0.5 h before bedtime	-	0.08	120	-	29.94	-	-
	0.3				0.22	120	-	57.36	-	-
	3				1.37	120	-	466.74	-	

Abbreviations: C_{max}, maximal plasma/serum concentration; IR, immediate release; T_{max}, time to maximal plasma/serum concentration; $t_{1/2\beta}$, elimination half-life; AUC, area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, AUC_{0-t}, unless marked with (*), which denotes $AUC_{0-\infty}$); Cl/F, apparent clearance; F, bioavailability.
The symbol (–) refers to studies not reporting the pre-defined PK variable or not reporting a mean/median-data value of the specific variable.

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

- C_{max} ranged from 0.05 ng/ml (0.1-mg dose, capsule, IR dosage form, [redacted]) to 101.16 ng/ml (dose 100 mg, gelatine-capsule, IR, [redacted]. Taking into account all preparations, the mean (±standard deviation [SD]) C_{max} was 5.24 (±15.31) ng/ml, while taking into account only the IR preparations, this was 5.64 (±16.65) ng/ml.
- T_{max} for the oral formulations ranged from 15 min (dose: 2 mg, gelatine-capsule, IR, [redacted] to 540 min (dose 2.5 mg, IR capsule, [redacted] Taking all values together both from SR and from IR formulations, the median T_{max} after oral administration was 60 min. Eliminating the SR formulations, the median T_{max} of the IR ones remained at 60 min. Actually, a T_{max} of melatonin being ~ 30-60 min seems well-established from the literature [redacted]
- $t½_{\beta}$ ranged from 32 min (dose 2 mg, gelatine capsule, IR, [redacted]) to 126 min (dose 4 mg, oral tablet preparation with 25% dose IR release and 75% dose controlled-release, [redacted], or when taking into consideration only IR formulations, 106 min (dose 6 mg, tablet IR, [redacted]. The mean (±SD) for all oral preparations was 57 (±25) min while only for the IR ones, this was 49 (±17) min. Actually, a t½ of melatonin being ~45min is well-established in the literature [redacted]
- AUC ranged between 12.79 ng×min/ml (dose 0.1 mg capsule, IR dosage form, [redacted] to 31.30×10^3 ng×min/ml (dose 3×80 mg, gelatine capsule, [redacted] or 27.87×10^3 ng×min/ml (dose 80 mg, gelatine capsule, [redacted] Taking all formulations into consideration, the mean (±SD) was 1.7×10^3 ($\pm6.2\times10^3$) ng×min/ml while only for IR formulations mean (±SD) was 1.9×10^3 ($\pm6.8\times10^3$) ng×min/ml.

Here, it is necessary to focus on those administering **oral melatonin in an IR formulation at daily doses of 0.5-6.0 mg**. The isolation of these studies (Table 2) was based on evidence of posology from clinical trials of melatonin for the treatment of jet lag and SWD as well as in sleep disorders in ADHD (paediatric) patients that are presented in Section *'2.5.4 Overview of Efficacy'* of the current Clinical Overview.

Table 8. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin IR formulations in conventional dosage forms (tablets and capsules); the doses ranged from 0.5 to 6 mg.

Reference	Dose (mg)	Dosage form	Time of intake	Dosing condition	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	F (%)
[redacted]	2.0	Gelatine capsule	10:00	Fasted	2.80	15	32	222.72	13.6
				Fed	6.80	30	-	482.16	29.6
	5.0	Tablet	Morning	Fasted	12.40	37.5	51.9	1,179.23(*)	28.9
	2.0	Tablet	07:00-09:00	Fasted	2.18	52	61	237.77(*)	14.4
	4.0				5.77	60	65	530.57(*)	16.2
	6	Tablet	08:30	Fasted	4.48	60	106	-	-

Reference	Dose (mg)	Dosage form	Time of intake	Dosing condition	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	F (%)
[redacted]	6	Tablet	09:00	-	1.80	60	37	138(*)	2.8
	6	Tablet	09:00	Fasted (different age)	16.76	30	46	1,180	24.1
					16.44	53	52	1,240	25.3
	0.5	-	-	-	-	-	47	-	33.0
	1.0	Capsule	11:45	-	0.40	135	-	95.94	11.7
	5.0	-	10:00	-	2.18	-	-	372	9.1
	5.0	Capsule	-	-	4.82	30	38	256.89(*)	6.3
	0.5	Capsule	0.5 h before sleep	-	0.84	30	42	134.28	32.9
			4 h after bedtime		0.70	60	42	78.81	19.3
	3.0	Capsule	09:30	-	0.68	60	68.4	99.78	4.1
	1.0	Capsule powder	-	-	0.80	60	-	90.5	11.1
		Soft-gelatine capsule	-	-	2.62	60	-	283.2	34.7
	3.0	Capsule powder	-	-	2.40	40	-	269.1	11.0
	2.5	Capsule	23:00	-	3.17	540	-	635.15	31.1
	3.0	-	09:30	-	3.56	20	-	-	-
	5.0	Capsule	0.5 h before sleep	-	2.05	120	-	426.47	10.4
	3.0	Capsule	0.5 h before bedtime	-	1.37	120	-	466.74	19.0

C_{max}: maximal plasma/serum concentration, T_{max}: time to maximal plasma/serum concentration, $t_{1/2\beta}$: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, AUC_{0-t}, unless marked with (*), which denotes $AUC_{0-\infty}$), Cl/F: apparent clearance, F: bioavailability. The symbol (−) refers to studies not reporting the pre-defined PK variable, or not reporting a mean/median-data value of the specific variable. Almost F (%) values were calculated based on the study of [redacted], where 2 mg of melatonin IV bolus were administered and resulted in a mean (±SD) $AUC_{0-\infty}$ 1,631.61 (±425.74) ng×min/ml. **F (%) values in bold were directly retrieved from the cited reference.**

Therefore, after oral administration of **IR melatonin formulation in doses ranging from 0.5-6.0 mg (Table 8)**:

- C_{max} ranged from 0.40 ng/ml (dose 1.0 mg, [redacted] *1994*) to 16.76 ng/ml (dose 6.0 mg, [redacted] with a mean (±SD) value 4.3 (±4.7) ng/ml.

- T_{max} ranged from 15 min (dose 2.0 mg, [redacted] to 540 min (dose 2.5 mg, [redacted] with a median value of 60 min. By eliminating this extreme high value that could represent an outlier, the maximum value of T_{max} is 135 min (dose 1.0 mg, [redacted] and the median value 56.5 min. It should be noted that the latter median is also closer to the mean T_{max} value referred in the literature which is 30-50 min [redacted] Moreover, as observed after reviewing the efficacy studies the best outcome is achieved when melatonin is administered 30-60 min before bedtime, which coincides with its T_{max}.

- $t_{1/2\beta}$ ranged from 32 min (dose 2.0 mg, [redacted] to 106 min (dose 6.0 mg,

[redacted] with a mean (±SD) value 53 (±19) min. Actually, a $t_{1/2}$ of melatonin being close to 45-60 min is well-established in the literature [redacted]

- AUC ranged from 78.8 ng×min/ml (dose 0.5 mg, [redacted]) to 1,240 ng×min/ml (dose 6.0 mg, [redacted], with mean (±SD) value 421 (±362.4) ng×min/ml.

- F (%) bioavailability (estimated from the literature data), ranged from 2.8% (dose 6.0 mg, [redacted]) to 34.7% (dose 1.0 mg, [redacted]) with a mean (±SD) value 18.5 (±10)%.

After having distinguished only the most relative PK studies with the intended dosing and formulation, it can be observed that **variability of PK parameters is relevantly high.** Data from studies conducted at other strengths can be extrapolated to the 3 mg dose, since the PKs is linear. The 3-mg dose is a standard dose in many punlished clinical studies as well as approved SmPCs for many melatonin products. However, mainly due to the well-known first-pass effect that melatonin undergoes the bioavailability is rather low [redacted] The variable bioavailability of oral melatonin is therefore not related to the differing IR formulations but is due to the variability in the high first-pass metabolism process of melatonin.

Two studies investigating the PKs of melatonin after administration of an **oral solution IR formulation** have been identified in the scientific literature as well (Table 9). The one was performed in critically ill patients [redacted] and the other in healthy volunteers [redacted]

Table 9. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin oral solution doses ranging from 0.25 to 10 mg.

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

[redacted] estimated the absolute bioavailability of melatonin in 12 young healthy volunteers after administration at midday, on 2 separate occasions, i.e., 0.23 mg by IV infusion and 0.25 mg by oral solution. Melatonin PKs were compared with those obtained after the administration of 0.23 mg melatonin by IV infusion (at a rate of 250 ml/h). In healthy males, PK parameters were C_{max}=0.24 ng/ml, T_{max}=23 min, $t_{1/2}$=36 min, $AUC_{0\text{-}inf}$=14.16 ng×min/ml and the absolute bioavailability mean (±SD) was 8.6 (±3.9) %. In the female subjects, the PK parameters were C_{max}=0.62 ng/ml, T_{max}=23 min, $t_{1/2}$=45 min, $AUC_{0\text{-}inf}$ = 42.08 ng×min/ml, and the absolute bioavailability mean (±SD) was 16.8 (±12.7)%. The absolute bioavailability of melatonin ranged from 1% to 37% with a mean (±SD) of 8.6 (±3.9)% for males and 16.8 (±12.7)% for females [redacted]

A randomised placebo-controlled trial has demonstrated that exogenous administration of melatonin at a loading dose of 3 mg (as solution through feeding tube), followed by an hourly

dose of 0.5 mg, results in supraphysiological and sustained concentrations of serum melatonin during 12 h overnight in critically ill patients. These findings support the consideration that despite a first-pass effect or pharmacological interactions on the enteral absorption of melatonin in critically ill patients, the enteral administration has an excellent oral bioavailability. Oral solution of melatonin (10 mg) was also administered in 24 patients undergone a tracheostomy in a randomised, double-blind, placebo-controlled trial. Melatonin appeared to be rapidly absorbed from the oral solution and C_{max} values were higher than those reported for comparable doses in healthy individuals. After oral dosing, the C_{max} is affected by the solubility of melatonin in the formulation, alterations in bioavailability and clearance. Orally administered melatonin is subjected to an extensive 'first-pass effect', with bioavailability reported to be ~15%, although there is high variability due to factors, such as CYP1A2 activity and co-administration of inetarcting drugs [redacted]

More resently, a bioavailability study has been performed as an open label, single-treatment, single-period, single-dose study in normal, healthy, adult, male human subjects under fasting condition. The subjects received a single oral dose of 3 ml of the medicinal product Melatonin Orifarm 1 mg/1 ml solution resulting in a mean plasma C_{max} close to 8,800 pg/ml. This is approximately 150 times the nocturnal endogenous C_{max} of melatonin, though both endogenous- and exogenous C_{max}s showed considerable inter-individual variation [redacted]

It is important to note that **the bioavailability of the oral solution is comparable to those of the IR solid dosage forms**, being within the range and approaching the mean. However, T_{max} is somehow lower compared to what it was observed for the solid IR forms, as is expected for an oral solution, not having the limiting step of dissolution. In any case, melatonin has been approved both as solid and solution oral formulations claiming the same indications and posologies.

Overall, a generally low bioavailability of oral melatonin has been documented in a number of studies and was confirmed by the assessment conducted within above, fluctuating mainly from 3-36% [redacted] Bioavailability presented a significant intra-individual variability. Moreover, the administration of different formulations also probably accounts for the great differences observed in bioavailability. It is generally agreed that the low bioavailability is caused by a considerable first-pass metabolism in the liver [redacted] The other PK parameters (C_{max} and AUC) displayed extensive variation within and between studies. The variations may obviously relate to interindividual differences in drug absorption, distribution, metabolism and elimination but may also be confounded by substantial variability in study designs/analytical methods.

Other routes of administration

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

Table 10. Mean PK variables reported in the public domain scientific literature after IV, transdermal, intranasal and transmucosal administration of melatonin.

Reference	Dose (mg)	Dosage form	C_{max} (ng/ml)	T_{max} (min)	t½ (min)	AUC (ng×min/ml)	Cl/F (L/min)	V_d (L)
[redacted]	2.1	Transdermal	-	8.58h	-	-	-	-
	10	IV bolus	221.5	-	42.3	8.997.63	-	1.6
	100	IV bolus	1.251.5	-	46.2	54,685.97	-	2.0
	20	Transdermal	-	2.8-8 h	-	-	-	-
	100			1.1-6 h				
	5	Sublingual spray	17.20	42.5	54.0	-	-	-
	8	Transdermal	-	13 h	-	-	-	-
	0.5	Transmucosal		474				
	0.0005 mg/kg	IV prepubertal	-	-	40	15.05	3.30	185
		IV pubertal			47	18.00	2.70	173
		IV adults			47	22.61	2.03	135
	2	IV	96.85	-	60	1.63×10^3	-	-
	0.23	IV infusion (250 ml/h) male	1.25	113	36	15.29	1.57	73.1
	0.23	IV infusion (150 ml/h) female	1.69	110	41	21.84	1.09	53.8
	0.005	IV bolus			28	5.40	0.97	35
	0.02	IV (10 ml/h) infusion	0.072	-	45	-	0.97	63
	0.4	Intranasal	-	5	-	-	-	-
	0.2	IV		10				
	3.6	Transdermal nanoparticle gel in 9 cm2 skin area	-	15 h	7.5 h	-	-	-

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

Dose-dependency of bioavailability in the 0.5-5.0 mg oral dose rage

Based on the above considerations, the above reported PK studies were distinguished in 4 basic categories in order to roughly investigate the variability of the PK parameters where doses of the same magnitude were administered.

Table 11. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin IR formulations doses **0.5-1.0 mg** to healthy volunteers.

Reference	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t_{½β}$ (min)	AUC (ng×min/ml)	F (%)
[redacted]	0.5	-	-	47	-	33
	1.0	0.40	135		95.94	11.7
	0.5	0.84	30	42	134.28	32.9
		0.70	60	42	78.81	19.3
	1.0	0.80	60		90.50	11.1
		2.62	60	-	283.20	34.7
Min		0.40	30.00	42.00	78.81	11.10
Max		2.62	135.00	47.00	283.20	34.70
Mean		**1.07**	**60[a]**	**43.67**	**136.55**	**23.78**

Reference	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t½_{\beta}$ (min)	AUC (ng×min/ml)	F (%)
SD		**0.88**	**-**	**2.89**	**84.58**	**11.08**

Abbreviations: C_{max}: maximal plasma/serum concentration, T_{max}: time to maximal plasma/serum concentration, $t½_{\beta}$: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.
*Median value is reported for Tmax.

Table 12. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin IR formulations doses **2.0-2.5 mg** to healthy volunteers.

Reference	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	F (%)
[redacted]	2.0	2.80	15	32	222.72	13.6
		6.80	30	-	482.16	13.7
	2.0	3.50	30		237.18	14.5
		4.40	30	40	349.56	21.4
	2.0	2.18	52	61	237.77	14.4
	2.5	3.17	540	-	635.15	31.1
Min		2.18	15.00	32.00	222.72	13.60
Max		6.80	540.00	61.00	635.15	31.10
Mean		**3.81**	**30***	**44.33**	**360.76**	**18.12**
SD		**1.64**	**-**	**14.98**	**167.10**	**7.02**

Abbreviations: C_{max}: maximal plasma/serum concentration, T_{max}: time to maximal plasma/serum concentration, $t½_{\beta}$: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.
*Median value is reported for Tmax.

Table 13. Mean PK variables reported in the literature after single oral administration of melatonin IR formulations dose **3.0 mg** to healthy volunteers.

Reference	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	F (%)
[redacted]	3.0	2.40	40		269.10	11.0
	3.0	3.56	20	-	-	-
	3.0	1.37	120	-	466.74	19.0
Min		1.37	20.00	0.00	269.10	11.00
Max		3.56	120.00	0.00	466.74	19.00
Mean		**2.44**	**40***		**367.92**	**15.00**
SD		**1.10**	**-**		**139.75**	**5.66**

Abbreviations: C_{max}: maximal plasma/serum concentration, T_{max}: time to maximal plasma/serum concentration, $t½_{\beta}$: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.
*Median value is reported for Tmax.

Table 14. Mean PK variables reported in the scientific literature after single oral administration of melatonin IR formulations doses **6.0 mg** to healthy volunteers.

Reference	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	F (%)
[redacted]	5.0	12.40	38	52	1,179.23	28.9
	5.0	2.18	-	-	372.00	9.1
	5.0	4.82	30	38	256.89	6.3
	5.0	2.05	120	-	426.47	10.4
	6.0	4.48	60	106	-	-
	6.0	1.80	60	37	138[1]	2.8
	6.0	16.76	30	46	1,180	24.1
		16.44	53	52	1,240	25.3
Min		2.05	30.00	38.00	256.89	6.30
Max		16.76	120.00	106	1,240	28.90
Mean		**7.62**	**53***	**55.17**	**684.66**	**15.27**
SD		**6.1**	**-**	**23.5**	**454.28**	**9.73**

Reference	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\,\beta}$ (min)	AUC (ng×min/ml)	F (%)
Abbreviations: C_{max}: maximal plasma/serum concentration, T_{max}: time to maximal plasma/serum concentration, $t_{½\beta}$: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability. *Median value is reported for Tmax.						

Although it cannot be concluded with certainty, in a dose range of 0.5-6.0 mg IR, both C_{max} and AUC seem to be dose dependent, while absolute bioavailability seems not to be affected by dose.

PK linearity

In addition to the above information, it has been shown that **melatonin also exhibits linearity in PKs over the dose range of 0.1-10 mg.** In particular, there is a trend for a more than proportional increase by increasing the dose; however, it does not exceed the threshold of non-proportionality between the usual therapeutic range of 0.1-10 mg [redacted] The PKs is also linear in the lower dose ranges of 0.1-5 mg after oral administration of IR melatonin [redacted] Later, [redacted] showed linear PKs between 0.4 mg and 4 mg following following administration of two different oral surge-SR doses in older adults, which was also confirm by [redacted]. When administered IV, melatonin also exhibits linear PKs over the range of 0.01-5.0 µg/kg [redacted] Most of the reported melatonin oral products' SmPCs report PK linearity up to 8 mg. Based on the consideration of the body of published evidence as a whole, melatonin PKs may be considered linear at the range of 0.1-10 mg.

Food effect

Regarding the food effects, it seems that there is not enough evidence to strongly support its inexistence. It seems that it could be formulation-dependent as noticed in SR 2-mg melatonin [redacted] However, another literature review has presented a study that has determined plasma concentrations of melatonin under fed and fasting conditions. Melatonin concentrations were higher in the fed state compared to fasted state for both solid and liquid formulations tested, however T_{max} was sclose (for the solid capsules) and same (for the liquid form) for both prandial states [redacted]. In any case, the high variability of melatonin PK makes it rather impossible for these AUC differences to result in clinically significant alterations in efficacy or safety. However, most approved SmPCs for similar products recommend avoidance of food consumption 2 h before to 2 h after taking melatonin; this suggestion will be also proposed for this product.

2.5.3.1.2 Distribution

Melatonin is not strongly or extensively bound to plasma proteins, therefore, protein binding effects on PKs should not be expected to be significant. Indeed, the *in vitro* plasma protein binding of melatonin is about 60.0%. Melatonin is mainly bound to albumin, α_1-acid glycoprotein and high-density lipoprotein (HDL) [redacted] The level of melatonin binding appears to be constant over range of different serum concentrations. Literature data indicate that melatonin is distributed in all body fluids and is accessible at all tissues. The mean binding of melatonin to erythrocytes is 49.0%.

Melatonin reaches all tissues of the body within a very short period. Its t½ is bi-exponential, with a first distribution t½ of 1.4 min and a second of 28.4 min [redacted] Distribution from serum to saliva and passing through the BBB is rapid. Melatonin released to the CSF via the pineal recess attains, in the 3rd ventricle, concentrations up to 20-30 times higher than in blood. These concentrations, however, rapidly diminish with increasing distance from the pineal, thus suggesting that melatonin is taken up by brain tissue [redacted] IV bolus administration of [^{14}C]-melatonin was shown to rapidly cross the BBB, interact with brain structures and quickly disappear from the brain, which suggests rapid diffusion and turnover. In a human positron emission tomography (PET) study performed with [^{11}C]-melatonin in a healthy volunteer, analysis of tracer kinetics showed maximum activity in the brain at 8.5 min following injection, which was different from the curve observed for the plasma radioactivity (maximum at 3.5 min). This result confirmed that melatonin readily crosses the BBB and that 6-sulphatoxymelatonin is the main plasma metabolite. In this study, the distribution of tracer as a function of time, failed to reveal any specific binding [redacted]

It has been estimated that the mean steady state volume of distribution ($V_{d,ss}$) in healthy adult volunteers, following an IV infusion of D_7-melatonin, to be 0.98 L/kg distribution. No gender difference in the $V_{d,ss}$ normalised to body weight was observed; 0.99±0.063 L/h/kg and 0.97±0.13 L/h/kg in male and female subjects, respectively [redacted]

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

2.5.3.1.3 Metabolism

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

[redacted] used a panel of 11 recombinant human P450 isozymes to investigate for the first time the 6-hydroxylation and O-demethylation of melatonin. CYP1A1, CYP1A2 and CYP1B1 all 6-hydroxylated melatonin, with CYP2C19 playing a minor role. These reactions were NADPH-dependent. CYP2C19 and, to some extent CYP1A2, *O*-demethylated melatonin. The K_m (µM), i.e., the concentration of substrate that is transported at half the maximal velocity (V_{max}) of transport and V_{max} (k_{cat}, pmol/min/pmol P450) for 6-hydroxylation were estimated as 19.2±2.01 and 6.46±0.22 (CYP1A1), 25.9±2.47 and 10.6±0.32 (CYP1A2) and 30.9±3.76 and

5.31±0.21 (CYP1B1). These findings confirm the suggestion of others that CYP1A2 is probably the foremost hepatic P450 in the 6-hydroxylation of melatonin and a single report that CYP1A1 is also able to mediate this reaction. However, this is the first time that CYP1B1 has been shown to 6-hydroxylate melatonin. The 50% inhibitory concentration (IC_{50}) for the CYP1B1-selective inhibitor (*E*)-2,4,3',5'-tetramethoxystilbene was estimated to be 30 nM for melatonin 6-hydroxylation by recombinant human CYP1B1. Comparison of brain homogenates from wild-type and cyp1b1-null mice revealed that 6-hydroxylation of melatonin was clearly mediated to a significant degree by CYP1B1. CYP1B1 is not expressed in the liver but has a ubiquitous extrahepatic distribution and is found at high levels in tissues that also accumulate either melatonin or 6-hydroxymelatonin, such as intestine and cerebral cortex, where it may assist in regulating levels of melatonin and 6-hydroxymelatonin.

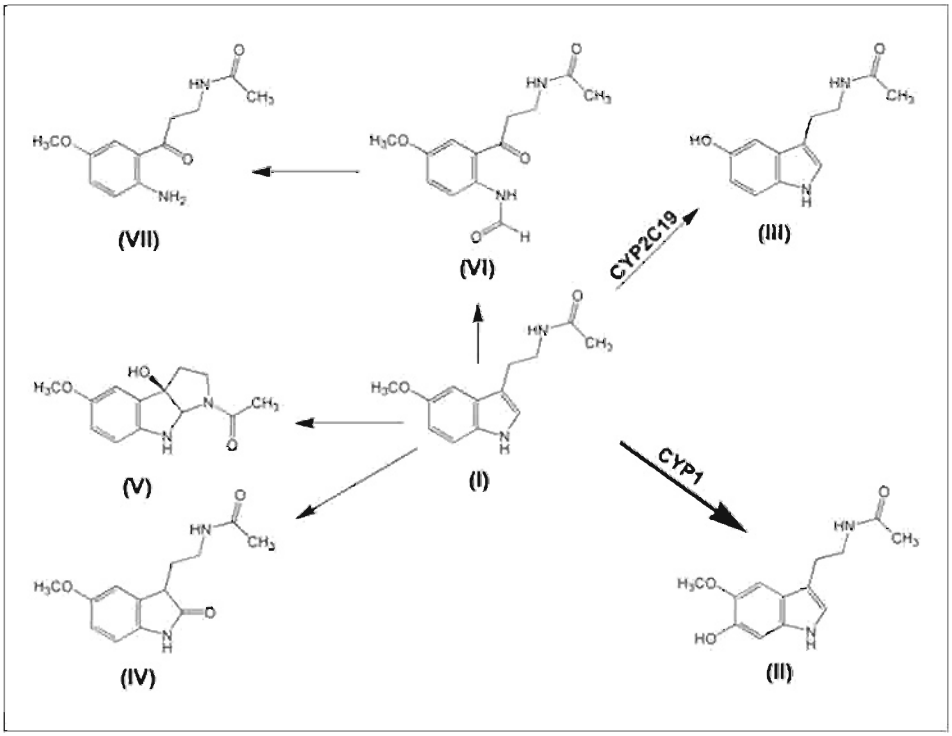

Figure 3. Biotransformation pathway of melatonin [redacted]

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

A markedly increased AUC for the ratio of 6-sulphatoxymelatonin to melatonin in plasma after oral as compared with IV administration (13±13 vs 1±1) has been found, which can be

explained only if one assumes that there was considerable first-pass hepatic extraction after oral administration (which converts melatonin to its metabolite before it enters the systemic circulation), giving rise to the conversion of melatonin to 6-sulphatoxymelatonin and thereby decreasing the bioavailability of the hormone [redacted]

A substantial fraction of melatonin is metabolised to kynuramine derivatives in the brain. This is of interest as the antioxidant and anti-inflammatory properties of melatonin are shared by these metabolites, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and, with considerably higher efficacy, N^1-acetyl-5-methoxykynuramine (AMK). AFMK is produced by numerous non-enzymatic and enzymatic mechanisms; its formation by myeloperoxidase appears to be important in quantitative terms [redacted]

2.5.3.1.4 Elimination

6-Sulphatoxymelatonin, the primary metabolite of melatonin, accounts for around 90% of the dose excreted in urine [redacted] The other main metabolite results from *O*-demethylation of melatonin, yielding *N*-acetylserotonin [redacted] Approximately 2% of the exogenous melatonin is excreted in an unchanged form. No figures are provided as to the extent of urine excretion of the secondary metabolite, mainly the glucuronide conjugate of 6-hydroxymelatonin. A $t_{½\beta}$ of ~45 min has been documented in several studies in a wide range of doses, up to 100 mg IV. This parameter may also be described by first-order elimination kinetics and is independent of dose and route of administration. In addition, approximately 1% of blood melatonin is excreted in urine without being metabolised. A positive correlation between AUC of melatonin and 6-sulphatoxymelatonin has been demonstrated in urine [redacted] The measurement of the main melatonin metabolite in urine seems to provide a robust, simple and reliable assessment of melatonin secretion. Over 90% of the administered radioactivity ([^{14}C]) was recovered in the first 24-h urine sample and the remainder in the next 24 h [redacted]

Following IV infusion of 23 µg D_7-melatonin, total body clearance in healthy males and females was 1.27±0.20 L/h/kg and 1.18±0.222 L/h/kg, respectively [redacted] The t½ of melatonin following single IV and oral doses in healthy volunteers has been reported to be ~1 h [redacted] In another study, the $t_{½\beta}$ has been reported as 43.6 min after IV administration in human subjects [redacted] The t½ following an IV infusion to be 36.0 and 41.4 min in male and female subjects, respectively, and after oral dosing, 36.0 and 45.0 min, respectively [redacted]

In a population PK turnover and surge-function study, describing the circadian disposition of melatonin in healthy male subjects, the $t_{½\beta}$ was estimated to be 2.7 h, i.e., longer than 0.5-1.0 h reported after exogenous IV and oral melatonin administration to healthy adults. This difference may reflect the continuous formation and release of melatonin while hormone synthesised earlier was undergoing elimination from the bloodstream, thereby leading to an underestimation of the terminal phase slope [redacted]

2.5.3.1.5 Pharmacokinetic studies in special populations

Age and gender

As previously described, melatonin is rapidly metabolised by the liver and eliminated in the urine as 6-sulphatoxymelatonin; therefore, the urinary excretion of this melatonin metabolite can serve as a reliable measure of serum melatonin profile. Serum melatonin concentrations decrease as age increases. It has been reported that in healthy elderly people suffering from insomnia, urinary 6-sulphatoxymelatonin was significantly lower and its onset and T_{max} delayed, in comparison to age-matched controls without sleep disorders. Similarly, in elderly females, 6-sulphatoxymelatonin levels were found to be significantly lower in poor compared to good sleepers ([redacted] measured the magnitude and duration of melatonin secretion over a 25-h period, following administration 250 µg of D_7-melatonin at midday and at midnight in 2 separate studies and 2 groups of subjects, i.e., 12 young (26.7±4.4 years) and 11 older men and women (70.0±3.3 years). For all subjects, endogenous melatonin concentrations were lower than 0.5 pg/ml between 10:00 and 18:00. A rapid rise was observed for all subjects and steady state was reached in, 3-4 h (3 or 4 t½s). Secretion started at 20:10±50 min (19:15-21:25 h) and 20:40±40 min (19:50-21:45 h) in young men and women, respectively. Offset of secretion was at 04:05±50 min (range, 03:05-05:25 h) and at 04:20±35 min (range, 03:35-05:10 h) for men and women, respectively. No significant gender difference in duration of secretion (7.9±0.8 h and 7.6±0.8 h), C_{max} (54.7±23.1 and 54.2±26.4 pg/ml) and AUC (375.5±178.6 and 349.7±174.8 pg×h/ml) was observed. The terminal t½ values, 1.2±0.3 h and 1.1±0.5 h, determined by regression of the terminal portion of the log-plasma concentration-time profile, showed no significant gender difference. There was also no significant gender difference in the amount of nocturnal secretion normalised to body weight of subjects; 0.48±0.23 and 0.40±0.19 µg/kg in men and women, respectively. Steady state melatonin concentrations were equal to 47.2±20.4 pg/ml (range: 17.0-85.7) and 46.3±25.5 pg/ml (range: 18.7-91.5) in men and women, respectively, with no significant gender difference.

In a randomised, double-blind, placebo-controlled study, low (0.4 mg) and high (4 mg) doses melatonin (25% IR + 75% controlled-release) were given in 27 older adults with insomnia complaints and low endogenous melatonin levels. The T_{max} (1.3 h vs 1.5 h), $t_{½\beta}$ (1.8 h vs 2.1 h) and apparent total clearance (379 L/h vs 478 L/h) did not differ significantly between the low- and high-dose arms, respectively. C_{max} values were 405±93 pg/ml for the low- and 3,999±700 pg/ml for the high-dose arm, both of which are substantially higher than physiologic melatonin levels for this age group. In addition, subjects in the high dose arm maintained melatonin levels >50 pg/ml for an average of 10 h, which could result in elevated melatonin levels beyond the typical sleep period. Renal and liver function parameters remained stable after 6 weeks of treatment. A linear PK behaviour of melatonin was demonstrated in the group of older patients [redacted]

Overall, the PKs of IR melatonin in the range of 0.3-6 mg is generally comparable in younger and older adults, through the range of values for a given parameter tends to be greater in the elderly. There do not appear to be significant differences in the PKs of oral melatonin in men and women, though C_{max}, AUC and bioavailability may be higher in women; no such tendency

is evident for t½. Data for the influence of race and genetic factors are limited but are not considered to suggest any major concerns for efficacy or safety [redacted]

Paediatrics

For the determination of the potential changes of melatonin PKs during puberty, melatonin was infused IV in 9 prepubertal (aged 8.4±1.5 years), 8 pubertal (aged 12.9±1.7 years) and 16 adult subjects. A pilot study of 3 adult males showed dose linearity, absence of saturation kinetics and unaltered metabolism and urinary excretion for doses of 0.1, 0.5 and 5.0 µg/kg. All other subjects received 0.5 µg melatonin/kg body weight. The results of the PK parameters calculated from serum melatonin showed no significant gender differences in adults. However, developmental differences were significant between prepubertal children and adults for terminal elimination rate constant (k_e, 1.08±0.25 vs 0.89±0.11 h^{-1}), $t½_\beta$ (0.67±0.12 vs 0.79±0.10 h) and AUC (250.9±91.8 vs 376.9±154.3 pg×h/ml, respectively). At all timepoints, melatonin levels were higher in serum than in saliva and the ratio between serum and salivary melatonin varied up to 55-fold within and between individuals. Results based on salivary melatonin showed significant differences between prepubertal children and adults for the k_e (1.90±0.95 vs 1.06±0.28 h^{-1}). The described group differences in PK parameters suggest that prepubertal children metabolise melatonin faster than adults [redacted]

[redacted] assessed the PKs of melatonin (0.5 mg/kg) enteral administration to 5 neonates with hypoxic-ischaemic encephalopathy undergoing hypothermia. Infusion started 1 h after the neonates reached the target temperature of 33.5°C. The plasma C_{max} reached 0.25 µg/ml and the AUC_{24h} was 4.35 µg×h/ml. In addition, the t½ and clearance of melatonin were prolonged, whereas V_d decreased compared to adults. *In silico* simulation estimated that the steady state can be reached after 4 infusions. Hypothermia did not affect melatonin PKs [redacted]

Hepatic impairment

Plasma melatonin levels have been studied in 7 patients with cirrhosis and 7 age-, sex- and education-matched controls. Patients with cirrhosis and subclinical hepatic encephalopathy had abnormal plasma melatonin pattern compared with healthy controls [redacted] The time of onset of melatonin secretion was significantly displaced from 19:50±26 to 21:30±13 min (P=0.013). T_{max} for plasma melatonin was significantly displaced from 00:36±33 to 05:36±29 min. Significant increases in absolute melatonin levels were seen during day- and night-time hours (P<0.05 at every measurement between 02:30 and 10:00).

In a later study, urinary 6-sulphatoxymelatonin levels were measured in 21 hospitalised cirrhotic patients with normal renal function (14 men and 7 women; median age [range]: 50 [29-80] years; Child class A, 7 patients; class B, 11 patients; class C, 3 patients) and in 9 healthy subjects (3 men and 7 women; median [range] age: 49 [32-69] years). Sixteen had alcoholic liver disease, 2 had hepatitis C and 1 each had primary biliary cirrhosis and Wilson disease; also, 2 patients had signs of clinically overt hepatic encephalopathy. Eight-hour urine excretion (22:00-06:00) was assayed for 6-sulphatoxymelatonin and finally cirrhotic patients had a significantly decreased concentration (mean±standard error [SE], 19.01±2.76 compared with 39.2±5.41 ng/ml; P=0.001) and total excretion (median [range]: 8.28 [0.85-28.1] mg vs 12.21

[9.12-29.04] mg; $P<0.05$) of 6-sulphatoxymelatonin, compared with controls. Urine volumes were similar in the 2 groups. No correlation to child class or liver function measures was seen. These findings indicate that the elevated plasma melatonin levels seen in cirrhotic patients are at least partly due to impaired hepatic catabolism [redacted] Another study concluded that the elevated melatonin blood levels both at night and day may account for some of the clinical manifestations of hepatic encephalopathy (daytime sleepiness, fatigue) [redacted]

Renal impairment

Literature data indicate that there is no accumulation of melatonin after repeated dosing (3 mg for 5-11 weeks) in patients on stable haemodialysis. However, as melatonin is primarily excreted as metabolites in the urine, plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment. The melatonin status of patients in end-stage chronic renal failure (CRF) has been evaluated by determining daytime plasma melatonin levels and investigating the circadian rhythmicity of melatonin secretion [redacted] A significant increase in plasma melatonin concentration was found in all investigated CRF patient groups, i.e., CRF patients on conservative treatment (n=48), CRF patients on maintenance haemodialysis treatment (n=39) and CRF patients on peritoneal dialysis (n=32). Successful transplantation led to a marked reduction in plasma melatonin levels. The circadian rhythm of melatonin secretion also appeared to be suppressed in CRF as the nocturnal secretory surge was absent in all haemodialysis and in 80% of the post-transplantation patients. Another study on patients with end-stage renal disease on haemodialysis demonstrated that melatonin plasma concentrations were not affected by the process, suggesting that haemodialysis could eliminate melatonin [redacted] Thus, it appears that renal insufficiency affects melatonin elimination and is not compensated by haemodialysis.

Pregnancy

Melatonin has protective actions on both the fetus and the mother during pregnancy. It can easily cross the placenta to enter the fetal circulation leading the photoperiodic information to the fetus. Melatonin levels were found to be decreased in severe pre-eclampsia. Some recent evidence has suggested supplements of melatonin to prevent pre-eclampsia in humans [redacted]

Lactation

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

One study found that breast-milk melatonin concentration was inversely correlated with breast-milk prolactin level and was higher in women experiencing fatigue in the morning [redacted] Five nursing mothers provided breast-milk samples every 2 h over a 24-h period. Melatonin was undetectable during the day, but began to rise at about 8:00, reaching a peak at about 3:00 and then declining [redacted]

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

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

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

Infant levels: A study of 8 breastfed and 6 formula-fed infants found different patterns of the melatonin metabolite, 6-sulphatoxymelatonin, in urine. Breastfed infants had a sinusoidal excretion pattern with a peak at 06:00 and a trough at 18:00. Formula-fed infants had a simple increase in the metabolite that was at baseline between about 20:00 and 04:00 with a peak at about noon [redacted]

PK-PD studies

Based on its mechanism of action as a chronobiotic, the response of the body to melatonin follows a phase-response curve (PRC), so that morning administration causes a delay, while evening administration causes an advance on circadian rhythms. This PRC is about 12 h out of phase with the PRC to light which causes a phase advance in the morning and a phase delay in

the evening [redacted] The shift of the circadian rhythm induced as depicted in the PRC is a PD marker that may be considered indicative of melatonin's efficacy in the treatment of jet lag. A number of studies have investigated the PRC produced after administration of exogenous melatonin at a specific time and after subtraction of the baseline PRC estimated before administration [redacted]. This is also supported by the fact that **the observed differences on the effects of melatonin in relation to administration time are** not due to differences in PKs but probably due to a difference in the **concentration of endogenous melatonin and in the phase of circadian human rhythm** [redacted]

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

In an attempt to investigate the potential dose-relationship when administering exogenous melatonin [redacted] evaluated the phase shift and the induced change in core body temperature. Following administration of 0.5- and 3.0-mg melatonin doses at the same clock times over 4 pulses (days), 3.0- and 3.9-h phase advances were observed, respectively. As for the shifting in the temperature minimum to occur within afternoon/evening was achieved by 73% of the volunteers receiving 3 mg and 56% of those taking 0.5 mg of melatonin. A previous study established a dose-response relationship with IR 0.5-5.0 mg melatonin, by evaluating the phase shift induced, sleep onset, sleep quality and the core body temperature (Table 15). In this study, in 6 healthy volunteers took a non-conventional oral dosage form consisting of a milk suspension of a corn-oil melatonin preparation [redacted]

Table 15. PK-PD relationship of melatonin [redacted]
Abbreviations: C_{max}, maximal plasma/serum concentration; T_{max}, time to C_{max}; $t_{½\beta}$, elimination half-life; AUC, area-under-the-curve plasma/serum concentrations; (*) Acute effects on core body temperature suggest that the half-maximal response occurs in these concentrations [redacted]

Dose (mg)	Administration time (h)	T_{max} (min)	C_{max} (pg/ml)	$t_{½\beta}$ (min)	Plasma concentration at maximum response (*) (pmol/L)	Phase advance (h)
0.05	17:00	30	118	64.8	~430	0.36
0.50		60	1,327	42.6	~4,300	0.69

Dose (mg)	Administration time (h)	T_{max} (min)	C_{max} (pg/ml)	$t½_{\beta}$ (min)	Plasma concentration at maximum response (*) (pmol/L)	Phase advance (h)
5.00		30	18,495	70.2		1.43

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

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

In the study of [redacted], the salivary samples contained >300 pg/ml melatonin 1 h after administration of 3-mg melatonin, which is in accordance with previous PK findings proving that the maximum levels of melatonin and thus maximum effects are noticed about 1 h post-dose. Thus, the plasma levels achieved with an IR dosage form about 1 h post-administration may be indicative of its efficacy (Table 16).

Table 16. Plasma concentrations produced 1 h after melatonin administration as a single IR oral formulation (data from [redacted]

Dose (mg)	Plasma levels (pg/ml)
0.1	50
0.3	120
1.0	400
2.0	1,900
10.0	6,300
80.0	25,800

However, there is no direct dose-response relationship, especially in terms of jet lag management or phase shifting, probably due to the inherent variability of circadian rhythms among humans [redacted]. A non-linear dose response in melatonin PRC with only ~40% increased amplitude for a 500% larger dose has been demonstrated [redacted]. Based on dose-response

studies evaluating sleep onset, it was proved that MTs are saturated at levels >200 pg/ml, as doses from 0.3 to 10.0 mg produced effects of similar magnitude [redacted]

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

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

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

2.5.3.2 PHARMACODYNAMICS

Melatonin is involved within the whole circadian system and influences the induction of sleep; it is secreted at night by the pineal gland located behind the 3rd ventricle in the brain with daily and seasonal rhythms mainly under the control of the circadian oscillator located in the suprachiasmatic nucleus (SCN) where MTs are present [redacted] It is released into the blood and cerebrospinal fluid (CSF). Melatonin is synthesised in several other structures (retina, Harderian gland, gut) as well where the genetic expression and biochemical activity of the melatonin-synthesising enzymes have been detected. During the day, plasma melatonin levels are low; at night, they rise 10 to 100-fold or more in young adults, but by considerably less in older people who often may have frequent nocturnal awakenings as a consequence. Very small oral melatonin doses raise daytime plasma melatonin to night-time levels, thus making it easier for people to fall asleep in the afternoon or evening. Such doses can also help older people remain asleep during the night. Circulating melatonin is mostly 6-hydroxylated by hepatic P450 monooxygenases and excreted as 6-sulphatoxymelatonin. Pyrrole-ring cleavage is of higher importance in other tissues, especially the brain. The product, N^1-acetyl-N^2-formyl-5-methoxykynuramine, is formed by enzymatic, pseudoenzymatic, photocatalytic, and numerous free-radical reactions. Additional metabolites result from hydroxylation and nitrosation. The secondary metabolite, N^1-acetyl-5-methoxykynuramine, supports mitochondrial function and downregulates cyclooxygenase (COX)-2. Antioxidative protection, safeguarding of mitochondrial electron flux and in particular, neuroprotection, have been demonstrated in many experimental systems. Melatonin has also occasionally been claimed to confer other medical benefits, e.g., preventing such age-related diseases as atherosclerosis, cancer and Alzheimer's disease [redacted]

2.5.3.2.1 Mechanism of action

Melatonin, a derivative of tryptophan, is a natural indoleamine hormone produced (from serotonin) by the pineal gland of humans and other mammals; chemically, it is not related to the steroid or peptide hormones. Tryptophan is first 5-hydroxylated (by tryptophan hydroxylase) and then decarboxylated (by aromatic L-amino acid decarboxylase) to form 5-hydroxytryptamine or serotonin (Figure 4). During daylight hours, the serotonin in pinealocytes tends to be stored and is unavailable to enzymes (monoamine oxidase [MAO] and the melatonin-forming enzymes) that would otherwise act on it. With the onset of darkness, postganglionic sympathetic outflow to the pineal increases and the consequent release of norepinephrine onto pinealocytes causes stored serotonin to become accessible for intracellular metabolism [redacted]

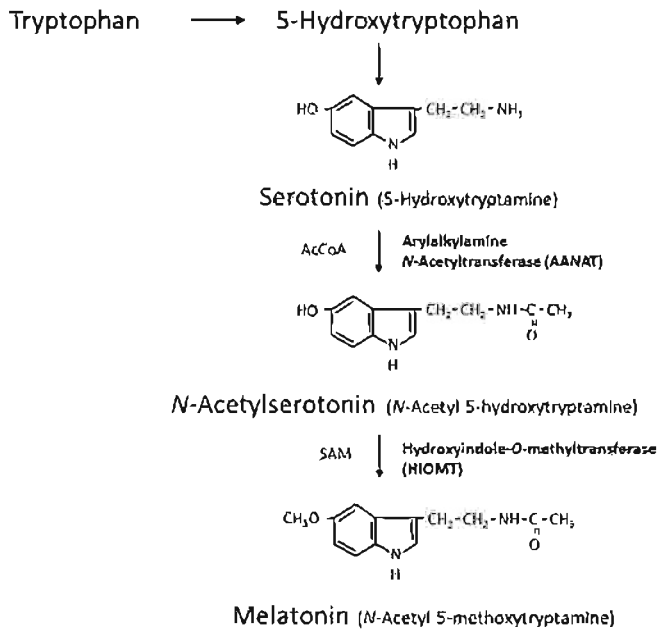

Figure 4. Pathway of melatonin synthesis in the pineal gland [redacted]

At the same time, norepinephrine activates the enzymes that convert serotonin to *N*-acetylserotonin and then to melatonin, especially serotonin-*N*-acetyltransferase and hydroxyindole-*O*-methyltransferase [redacted] Consequently, pineal melatonin levels rise manifold and then diffuses out of the pineal gland into the blood stream and CSF, rapidly raising human plasma melatonin levels from about 2-10 to 100-200 pg/ml. Melatonin binds to MT type 1A, which then acts on adenylate cylcase and the inhibition of a cyclic adenosine monophosphate (cAMP) signal transduction pathway. Melatonin not only inhibits adenylate cyclase, but it also activates phospholipase C (PLC); this potentiates the release of arachidonate. By binding to MTs 1 and 2, the downstream signallling cascades have various effects in the body. The MTs are G protein-coupled receptors (GPCRs) and are expressed in various tissues of the body. There are two subtypes of the receptor in humans, the MT1 and MT2. Melatonin and MT-agonists, on market or in clinical trials, all bind to and activate both receptor types, causing numerous physiological processes. MT1 receptors are expressed in many regions of the CNS, i.e., SCN, hippocampus, substantia nigra, cerebellum, central dopaminergic pathways, ventral tegmental area and nucleus accumbens. They are also expressed in the retina, ovary, testis, mammary gland, coronary circulation and aorta, gallbladder, liver, kidney, skin and the immune system. MT2 receptors are expressed mainly in the CNS, also in the lung, cardiac, coronary and aortic tissue, myometrium and granulosa cells, immune cells, duodenum and adipocytes. The binding of melatonin to MTs activates a few signaling pathways. MT1 receptor activation inhibits the adenylyl cyclase, and its inhibition causes a rippling effect of non-activation; starting with decreasing formation of cAMP, and then progressing to less protein kinase A (PKA) activity, which in turn hinders the phosphorilation of cAMP responsive element-binding protein (CREB binding protein) into P-CREB. MT1 receptors also activate PLC, affect ion channels and regulate ion flux inside the cell. The binding of melatonin to MT2 receptor inhibits adenylyl cyclase which decreases the

formation of cAMP. As well it hinders guanylyl cyclase and therefore the forming of cyclic guanosine monophosphate (cGMP). Binding to MT2 receptors probably affects PLC which increases PKC activity. Activation of the receptor can lead to ion flux inside the cell [redacted] *a*[redacted] Melatonin has a role in ocular pathophysiology. In addition to the pineal gland, melatonin synthesis is carried out in several ocular structures. Moreover, specific MTs have been located in the retina, cornea, ciliary body, lens, choroid and sclera, which suggests that cells in these tissues may be targets for melatonin action [redacted] The following Figure illustrates the basic mechanism of action of melatonin.

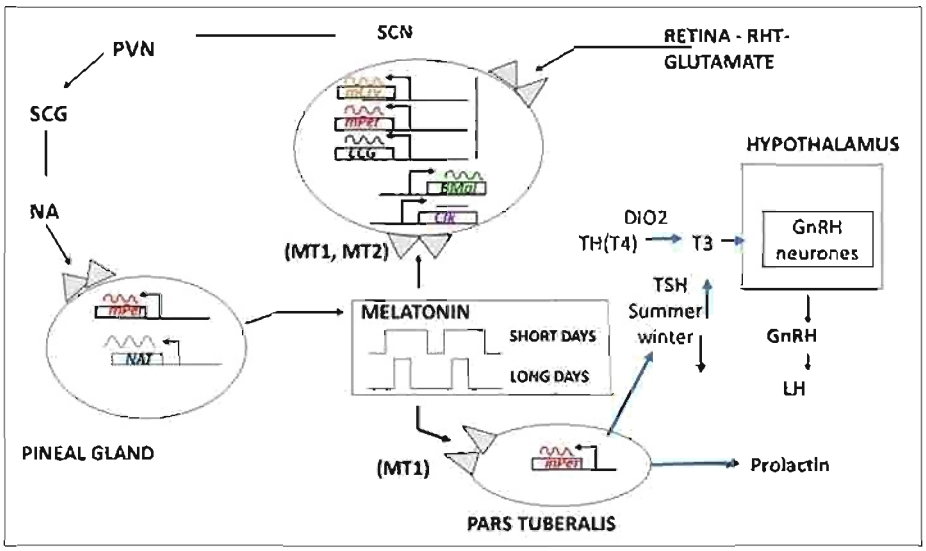

Figure 5. Diagrammatic representation of the control of production and the functions of melatonin, regarding seasonal and circadian timing mechanisms. **Abbreviations:** SCN: suprachiasmatic nucleus, PVN: paraventricular nucleus, SCG: superior cervical ganglion, NA: norepinephrine (noradrenalin), RHT: retino-hypothalamic-tract, CCG: clock-controlled genes [redacted]

Melatonin acts by 4 mechanisms in mammals, i.e., (i) binding to MTs in plasma membrane; (ii) binding to intracellular proteins such as calmoduline; (iii) binding to orphan nuclear receptors; (iv) antioxidant effect [redacted]

Melatonin interacts with intracellular proteins named calmoduline, calreticulin and tubulin. Calmoduline is an intracellular secondary messenger. Melatonin directly antagonises binding of calcium to calmoduline [redacted] The antiproliferative effects in cancer may be related to this. Retinoid-related orphan nuclear hormone receptor family (RZR/ROR) is responsible for the immunomodulatory effects of melatonin. Interleukin (IL)-2 and IL-6 are produced in mononuclear cells by this mechanism [redacted] There are 3 different membrane receptors and 1 nuclear receptor. In humans, MTs are also detected in several organs, including brain and retina, cardiovascular system, liver and gallbladder, intestine, kidney, immune cells,

adipocytes, prostate and breast epithelial cells, ovary/granulosa cells, myometrium and skin [redacted]

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

It is encoded in human chromosome #4 and consists of 351 amino acids *(Li et al., 2013)*. MT1 constitutes adenylate cyclase inhibition by binding to various G-proteins [redacted] MT1 receptors are commonly found in human skin. During aging process and Alzheimer's disease, the expression of MT1 in SCN and cortex decreases [redacted] MT1 receptors reduce the neuronal discharge rate in SCN and suppress prolactin secretion [redacted].

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

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

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

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

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

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

- *Melatonin-related Orphan receptor; 'X linked Orphan G-protein coupled' (GPR50: H9, ML1X)*

It is an X-linked inherited receptor, binding to G-protein. It is the orthologue of MT3, which is found in non-mammalian living creatures. This receptor's gene is located on the X chromosome (Xq28) and consists of 618 amino acids. It is present in all mammalians including humans. It does not have the characteristics of binding to melatonin; however, it is effective in binding of melatonin to MT1 [redacted] GPR50 is located in the brain and periphery and its natural ligand has not been defined yet. It has no affinity to melatonin, however, when it dimerises with MT1, it inhibits the melatonin signal [redacted]. GPR50 also posseses other functions apart from melatonin; it interacts with neurite outgrow inhibitor and TIP60 (glucocorticoid receptor signal co-activator and histone acetyltransferase) [redacted]

2.5.3.2.2 Pharmacodynamic effects

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

Circadian regulation of sleep

The neurons of the major circadian clock, the SCN of the hypothalamus, are normally active during the day and slow down at night. The activation of SCN neurons has an inhibitory effect on the pineal gland, defining a nocturnal pattern of melatonin secretion. If SCN neurons are activated at night, e.g., by environmental light perceived by the retina, melatonin production declines. Melatonin, in turn, can acutely attenuate the activity of SCN. This action of melatonin is likely to support a normal decline in the activity of the SCN at night, further promoting melatonin secretion and contributing to an overall increase in the amplitude of circadian body rhythms. A temporal and functional interplay between melatonin and SCN and their response to environmental light promote a temporal alignment of multiple circadian body rhythms with each other (internal synchronisation) and with the periodic changes in the environment (external synchronisation). In addition to an acute inhibition of SCN activity, melatonin administration can also produce a shift in the circadian phase of SCN activity, either advancing or delaying its onset. The direction of the phase-shift depends on the time of melatonin treatment, i.e., administration of melatonin in the late afternoon can advance the circadian

clock, while early-morning treatment can cause a phase delay [redacted] *In vitro* studies have suggested that a chronobiological effect of melatonin, i.e., the induction of circadian phase shift, is likely to be explained by its direct effect on SCN neurons via specific, most likely, MT2 receptor [redacted]. Although the magnitude of the melatonin-induced phase shifts can vary between the species, the overall phenomenon appears to be well-conserved. Such phase shifts in the circadian oscillation of SCN activity may change the physiological and behavioural rhythmicity of the entire organism, including the sleep-wake cycle, and can significantly affect the sleep quality in both nocturnal and diurnal species. In humans suffering from circadian sleep disorders, daily melatonin treatment can help to reinforce the circadian synchronisation with the environment and entrain the physiological rhythms to a 24-h cycle [redacted]

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

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

A subsequent study, involving healthy adults (25 males and 19 females; aged 19-45 years), demonstrated that afternoon melatonin, morning intermittent bright light and a gradually advancing sleep schedule advanced circadian rhythms almost 1 h/day, thus, producing very little circadian misalignment. In particular, there were 3 days of a gradually advancing sleep/dark period (wake time 1 h earlier each morning), bright light on awakening (four 30-min bright-light pulses of ~5,000 lx alternating with 30 min room light <60 lx) and afternoon melatonin, either 0.5 or 3.0 mg melatonin timed to induce maximal phase advances, or

matching placebo. According to the results, there were significantly larger phase advances with 0.5 mg (2.5 h, n=16) and 3.0 mg melatonin (2.6 h, n=13), compared to placebo (1.7 h, n=15). There was no difference between melatonin doses. Subjects did not experience jet lag-type symptoms during the 3-day treatment [redacted]

In a double-blind placebo-controlled parallel-group study of a 27-day forced desynchrony paradigm with a 20-h scheduled sleep-wake cycle, 36 healthy adults (aged, 18-30 years; 21 men and 15 women) received orally either melatonin (0.3 mg or 5.0 mg) or placebo, 30 min prior to each 6.67-h sleep episode during forced desynchrony. Both melatonin doses improved polysomnographically determined sleep efficiency from 77% in the placebo group to 83% for sleep episodes occurring during circadian phases when endogenous melatonin was absent. However, this remained below the average sleep efficiency of 88% observed during sleep episodes scheduled during the circadian night, when endogenous melatonin was present. Melatonin did not significantly affect sleep initiation or core body temperature. Melatonin appeared to maintain efficacy across the study and did not significantly affect percentages of slow-wave sleep or rapid eye movement (REM) sleep [redacted]

2.5.3.2.3 Effects on critical functions

Early evidence has indicated that melatonin has an immune-haematopoietic role. In animal studies, melatonin provided protection against gram-negative septic shock, prevented stress-induced immunodepression and restored immune function after a haemorrhagic shock. In human studies, melatonin amplified the antitumoural activity of IL-2; also, it has been proven as a powerful cytostatic drug *in vitro* and *in vivo*. In the human clinical field, melatonin appears to be a promising agent either as a diagnostic or prognostic marker of neoplastic diseases or as a compound used either alone or in combination with the standard cancer treatment. In the cardiovascular system, melatonin seems to regulate the tone of cerebral arteries; MTs in vascular beds appear to participate in the regulation of body temperature. Heat loss may be the principal mechanism in the initiation of sleepiness caused by melatonin. The role of melatonin in the development of migraine headaches is at present uncertain but more research could result in new ways of treatment. It is the major messenger of light-dependent periodicity, implicated in the seasonal reproduction of animals and pubertal development in humans. Multiple receptor sites detected in brain and gonadal tissues of birds and mammals of both sexes indicate that melatonin exerts a direct effect on the vertebrate reproductive organs. In addition, melatonin is one of the most powerful scavengers of free radicals. Because it easily penetrates the BBB, this antioxidant may be used for the treatment of Alzheimer's and Parkinson's diseases, stroke, nitric oxide, neurotoxicity and hyperbaric oxygen exposure. In the digestive tract, melatonin reduced the incidence and severity of gastric ulcers and prevented severe symptoms of colitis, such as mucosal lesions and diarrhoea [redacted]

Endocrine functions

As presented and discussed in the Non Clinical Overview (Module 2.4), results of a number of *in vivo* and *in vitro* experiments have demonstrated that the effect of melatonin on prolactin, luteinising hormone (LH) and follicle-stimulating hormone (FSH) synthesis and secretion depends on the animal species, age, sex, the concentration of the hormone and experimental conditions. Moreover, the melatonin-responsive arterior lobe of the pituitary is an intermediate

in the control of prolactin secretion, while the melatonin-binding sites of the mediobasal hypothalamus are involved in the gonadotropic response to melatonin [redacted]

In an early double-blind crossover clinical study, at two different times of year (spring and autumn), 12 healthy volunteers (10 men and 2 women in spring, minus 1 man in autumn) were administered an oral preparation of melatonin (2 mg in 5 ml corn oil) or placebo (vehicle only) daily, at 17:00 for 1 month (spring) or 3 weeks (autumn). In spring, the anterior pituitary hormones LH, prolactin, growth hormone (GH) together with the thyroid hormone thyroxine (T4), cortisol, testosterone and melatonin were measured at 1- to 6-h intervals for 24 h in plasma on the day after the last dose. In autumn prolactive, cortisol and melatonin levels were determined on the last day of treatment. Subjective fatigue, mood and sleep records were kept throughout the studies. Melatonin increased early evening fatigue and actual sleep but had no effect on mood. Melatonin administration had no effect on the concentrations or 24-h rhythm of LH, GH, T4, testosterone or cortisol. An earlier fall in the nocturnal prolactin was observed on both occasions. Overall, prolactin levels were higher in spring than in autumn. In 5 subjects, secretion of endogenous melatonin was advanced by 1-3 h following exogenous melatonin dosing [redacted]

A systematic review conducted by [redacted] evaluated available published studies about melatonin action on the ovarian granulosa/theca interna cells. Seven studies retrieved from the scientific literature databases about melatonin action on granulosa cells were selected. Based on the overall results, the following can be attributed to the hormone's effects: a) progesterone increase in culture medium; b) increased oestrogen production; c) antagonistic action on oestrogen; d) improvement in cell quality resulting in improved embryo and higher pregnancy rates; e) improved cell proliferation via mitogen-activated protein kinase; f) reduction of free radicals. Nevertheless, there are contrarian papers reporting a reduction in progesterone production when high doses of melatonin are administered. Melatonin interferes in sex steroid production, boosting progesterone output. Such an action may help improve oocyte quality.

The results of an early double-blind, randomised, crossover study have confirmed the nocturnal increase in melatonin could contribute to the patterns of oxytocin, vasopressin and GH release seen over 24 h. In that study, 8 healthy male volunteers (mean ± SD age: 21±0.5 years) received melatonin in doses of 0.05, 0.5 or 5.0 mg or placebo. Melatonin produced dose-dependent changes in circulating concentrations of oxytocin and vasopressin, the 0.5-mg dose being stimulatory, whereas 5.0 mg was inhibitory. These two doses stimulated GH release. There was no significant effect on prolactin or cortisol release [redacted]

[redacted] evaluated the secretion of melatonin, 17β-oestradiol and FSH in relation to body mass index (BMI) in 90 pre- and postmenopausal women. Subjects were divided into 3 equal groups, i.e., group I (control)-women without menstrual disorders, group II-postmenopausal women without change in appetite and body weight, group III-postmenopausal women experiencing increased appetite and weight gain. Compared to the control group, the level of melatonin and oestradiol was statistically lower. The FSH level was higher than in the groups of postmenopausal women. No significant correlation was found in all groups between the level of melatonin and the levels of oestradiol and FSH. A negative

correlation was found between 6-sulphatoxymelatonin excretion and BMI and a positive correlation was noted between the level of FSH and BMI, mainly in overweight women.

In studies involving blind humans, a single oral melatonin dose at bedtime suppressed nocturnal cortisol secretion. However, suppression could have been secondary to an improved sleep after melatonin in these experiments [redacted] examined whether melatonin exerts a similar inhibitory effect on hypothalamic-pituitary-adrenal (HPA) activity in 14 healthy young waking men, tested at bedtime, but kept awake throughout the experimental epoch. Thirty minutes after oral ingestion of 5 mg of melatonin, the activity of HPA-system was stimulated through a standard insulin-induced hypoglycaemia. Adrenocorticotrophin hormone (ACTH) and cortisol concentrations under basal conditions before insulin injection, as well as in response to insulin-induced hypoglycaemia, were almost identical for the melatonin and placebo control conditions ($P>0.5$). However, melatonin increased plasma prolactin level ($P<0.01$) and reduced systolic BP in the time interval following hypoglycaemia ($P<0.05$). It was concluded that melatonin *per se* has no substantially suppressing effect on HPA secretory activity, although such an effect can be gated by sleep-related processes.

Other representative studies demonstrating the potential endocrine effects following administration melatonin in men and women are presented and discussed in Section *'2.5.5.1.1 Safety in special populations'*, particularly in *'Fertility and reproduction'*.

Pregnancy and ageing

There is a growing consensus that the antioxidant and anti-inflammatory properties of melatonin are of great importance in preserving the body functions and homeostasis, with great impact in the peripartum period and adult life. Melatonin supplementation during pregnancy can reduce ischaemia-induced oxidative damage in the fetal brain, increase offspring survival in inflammatory states and reduce BP in the adult offspring. In adulthood, disturbances in melatonin production negatively impact the progression of cardiovascular risk factors and promote cardiovascular and neurodegenerative diseases. The most studied cardiovascular effects of melatonin are linked to hypertension and myocardial ischaemia/reperfusion injury, while the most promising ones are linked to regaining control of metabolic syndrome components [redacted]

Cardiovascular disorders

Substantial evidence supports the importance of endogenous melatonin in cardiovascular health and the benefits of melatonin supplementation in various cardiac pathologies and cardiometabolic disorders. Melatonin plays a crucial role in major pathological processes associated with heart failure including ischaemic injury, oxidative stress, apoptosis and cardiac remodeling [redacted]

Cancer

From the epidemiological research, it has been postulated that melatonin has significant apoptotic, angiogenic, oncostatic and antiproliferative effects on various oncological cells. Some anticancer mechanisms of melatonin action include stimulation of apoptosis, MT1 and

MT2 stimulation, parosurvival signal regulation, the hindering of angiogenesis, epigenetic alteration and metastasis. The use of melatonin as an adjuvant with chemotherapeutic drugs for the reinforcement of therapeutic effects has been discussed in the last decades [redacted]. Recently, interest has shifted towards the role of melatonin on tumour metastases. Due to the broad range of the actions of melatonin, the mechanisms underlying its ability to interfere with metastases are numerous and include modulation of cell-cell and cell-matrix interaction, extracellular matrix remodeling by matrix metalloproteinases, cytoskeleton reorganisation, epithelial-mesenchymal transition and angiogenesis [redacted]

GI tract

The GI tract is a major source of extrapineal melatonin. In some animal species, tissue concentrations of melatonin in the GI tract surpass blood levels by 10-100 times and the digestive tract contributes significantly to melatonin concentrations in the peripheral blood, particularly during the day. Some melatonin found in the GI tract may originate from the pineal gland, as the organs of the digestive system contain binding sites, which in some species exhibit circadian variation. Unlike the production of pineal melatonin, which is under the photoperiodic control, release of GI melatonin seems to be related to periodicity of food intake. Melatonin and melatonin binding sites were localised in all GI tissues of mammalian and avian embryos. Postnatally, melatonin was localised in the GI tract of newborn mice and rats. Phylogenetically, melatonin and melatonin binding sites were detected in GI tract of numerous mammals, birds and lower vertebrates. Melatonin is probably produced in the serotonin-rich enterochromaffin cells of the GI mucosa and can be released into the portal vein postprandially. In addition, melatonin can act as an autocrine or a paracrine hormone, affecting the function of GI epithelium, lymphatic tissues of the immune system and the smooth muscles of the digestive tube and as a luminal hormone, synchronising the sequential digestive processes. Higher peripheral and tissue levels of melatonin were observed not only after food intake but also after a long-term food deprivation. Such melatonin release may have a direct effect on the various GI tissues but may also act indirectly via the CNS. Melatonin can protect GI mucosa from ulceration by its antioxidant action, stimulation of the immune system and by fostering microcirculation and epithelial regeneration. It may reduce the secretion of pepsin and the hydrochloric acid and influence the activity of the myoelectric complexes of the gut via its action in the CNS. Tissue or blood levels of melatonin may serve as a marker of GI lesions or tumours. Therefore, it has a potential for a prevention or treatment of colorectal cancer, ulcerative colitis, IBS, children colic and diarrhoea [redacted]

2.5.4 OVERVIEW OF EFFICACY

In Europe, melatonin was available for many years as an unlicensed medication and in many different formulations (tablets, capsules and liquids) of variable dosages. It has been widely available as an OTC medicinal product [redacted] IR drug products are also authorised, including as indication the treatment of jet lag and SWD. In the US, synthetic melatonin has also been available as an OTC preparation. Food supplements also contain melatonin as sleep aids. Melatonin has been widely available to patients of the community as a food supplement used as a sleep aid. The different brands are specifically labelled with this claim. As already mentioned, following a request from the EC, the EFSA NDA Panel was asked to provide a scientific substantiation of a health claim in relation to melatonin and alleviation of subjective feelings of jet lag [redacted]. The claimed effect is "sleep-wake cycle regulation" and the target population is assumed to be the general population. In weighing the evidence, the Panel took into consideration the conclusions of the Cochrane review [redacted] which indicated that melatonin was effective in alleviating the subjective symptoms of jet lag. On the basis of the data presented, the Panel concluded that a cause-and-effect relationship has been established between the consumption of melatonin and alleviation of subjective feelings of jet lag.

In order to elaborate on melatonin's well-established use based on publicly available data also for the indications of SWD in adults and sleep disorders for paediatric patients with ADHD, a thorough literature review was performed, aiming to properly describe the relevant aspects regarding the efficacy and safety of the drug in those indications. In particular, published data were assessed in order to elucidate the time over which melatonin has been in use for the treatment of these conditions, the doses implemented, the degree of scientific interest in the use of the substance and the coherence of scientific evaluations.

2.5.4.1 JET LAG

In order to elaborate on the WEU of melatonin for the management of jet lag based on publicly available data, a thorough literature review was performed, aiming to properly describe the relevant aspects regarding the efficacy and safety of the active substance. Therefore, after a detailed evaluation of the literature, published data were assessed in order to elucidate the time over which melatonin has been in use for the treatment of jet lag and SWDs, doses implemented, the degree of scientific interest in the use of the substance and the coherence of scientific evaluations.

Excretion of melatonin from the pineal gland and its action on melanocytes have been known since its first *in vivo* isolation by A. Lerner. However, most importantly, it was identified that the first clinical studies evaluating its efficacy and safety in the treatment of jet-lag [redacted] have been published since the late '80s. Melatonin efficacy aspects are currently being reviewed as noticed in many reviews and meta-analyses of clinical trials identified [redacted] In addition, many published guidelines of medical organisations, associations and institutions promote the use of melatonin in the treatment of jet lag, namely the AASM, British Association for

Psychopharmacology, Health Canada, Mayo Clinic, the International Federation of Sports Medicine and the US National Academy of Sciences [redacted] A schematic representation of the flowchart for the selection of articles for the use of melatonin in jet lag is provided below.

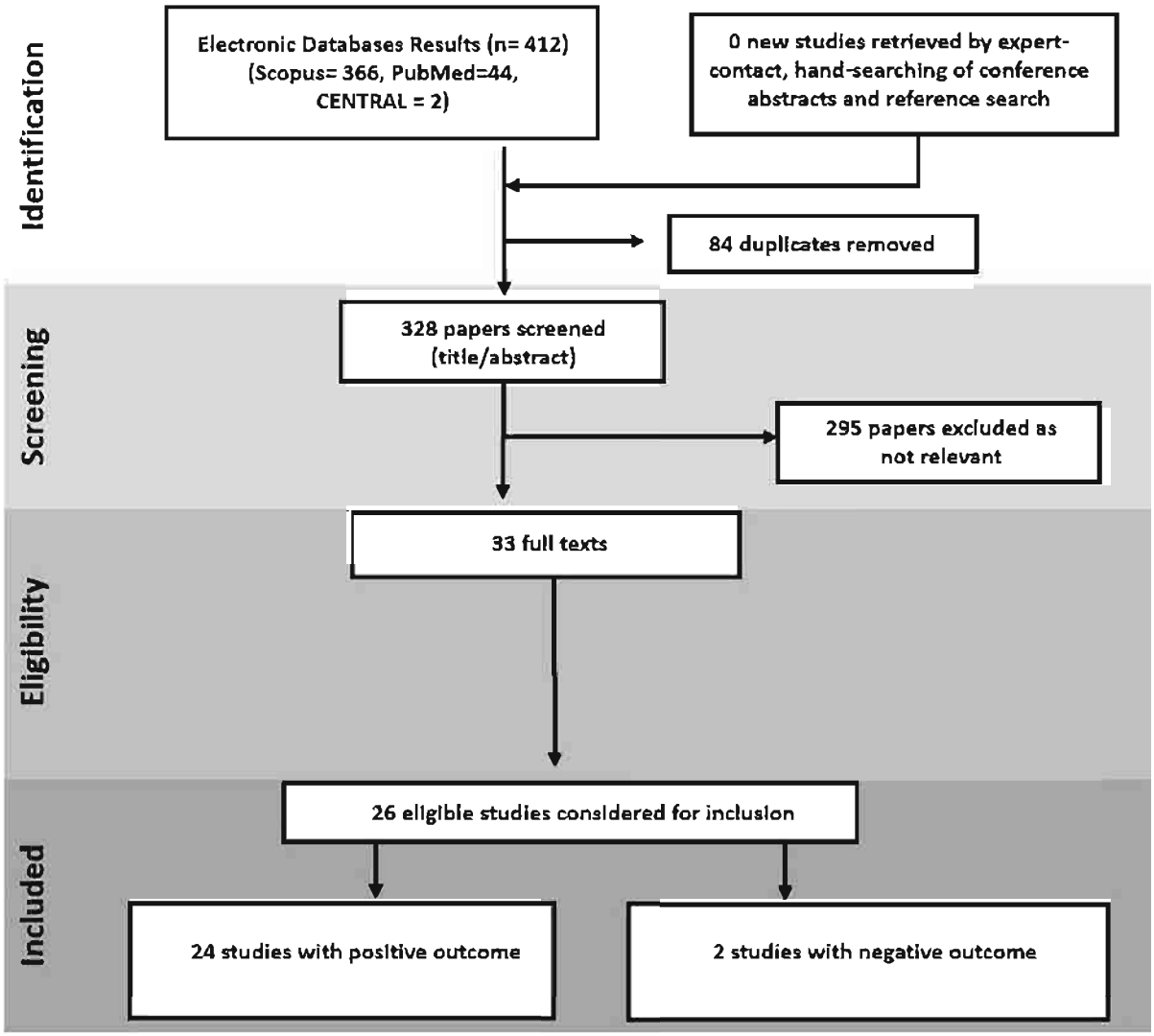

Figure 6. Flowchart for selection of articles (based on PRISMA general principles) for the use of melatonin in jet lag.

As depicted above, a thorough screening of the literature has identified 26 clinical studies dealing with the use of melatonin in jet lag (Table 17). Among them, 16 studies involving both eastwards and westwards travels concluded that melatonin is effective for the treatment of jet lag [redacted]

[redacted] 6 studies administered melatonin after inducing a phase shift [redacted] 2 studies concluded that melatonin is not effective for the treatment of jet lag [redacted], one study concluded that melatonin was effective only if its administration starts after travel [redacted]) and 1 study concluded that melatonin does not alleviate subjective jet lag but helps resynchronisation of cortisol levels when travelling eastwards [redacted]

Table 17. Published clinical studies investigating the efficacy of melatonin in the treatment of jet lag. Twenty-six studies found in the literature dealing with the use of melatonin in jet lag: 2 concluded that melatonin has not any effect (red), 2 concluded that melatonin is beneficial with a specific dosing scheme and under specific circumstances (yellow), 6 studies simulating phase shifts proved that melatonin helps resynchronisation (white) and 16 studies concluded that melatonin offers clinical benefits in the prevention, treatment, or alleviation of jet lag (green).

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

Reference	Study type	Doses	N	Time zones	Direction	Time of administration	Endpoints	Conclusion
[redacted]	Coss over placebo controlled	5 mg	36	6, 9 or 11	eastward	After flight at 23:00 local time of destination for 5 days, no pre-flight treatment	Subjective VAS of jet lag. Cortisol blood levels re-adaptation	Accelerated cortisol adaptation, non-significant VAS improvement
					westward			Not significant improvement compared to placebo
	Double blind randomised placebo controlled	8 mg	37	6-8	eastward	On flight day at 17-18:00 and after arrival at 22-23:00 local time for 3 days	Subjective VAS questionnaire on the global treatment efficiency, sleepiness., morning mood, fatigue, work performance	VAS of jet lag, sleepiness and sleep improved.
	Double blind placebo controlled	10 mg	29	8	eastward	For 3 days preflight at 15:30-16:00 (pre-bed at destination time), on flight day 15:30-18:00h and after arrival 30min pre-bedtime for 4 days (for 8 hours phase advance)	Sleep duration, cognitive performance, activity rhythms were recorded continuously for 13 days	Melatonin significnalty improved endpoints and helped resynchroniation.
	Double-blind randomised placebo controlled study.	0.5 mg IR, 5.0 mg IR, 2.0 mg CR	320	6-8	eastward	After flight once daily at bedtime for 4 days	Profile of Mood States (POMS), sleep log, Jet lag symptoms questionnaires, Karolinska Sleepiness Scale (KSS)	Melatonin improved jet lag. IR better than CR. Almost equal effects 0.5mg IR with 5.0mg IR. However, hypnotic properties of melatonin, sleep quality and sleep latency, were significantly greater with the 5.0-mg dose.
	Double-blind, randomised, placebo-controlled study	1) 5 mg melatonin 2)10 mg zolpidem 3)5mg melatonin + 10 mg zolpidem 4) placebo	137	6-9	eastward	After flight once daily at bedtime for 4 days	Daily sleep logs, Symptoms' questionnaires, Profile of Mood States (POMS), Subjective VAS for jet lag, Actigraphy	All 3 treatments led to a decrease of jet lag severity with zolpidem being the most effective treatment
	Double-blind placebo-controlled trial	5 mg	52	11-12	westward	1) **early melatonin group** (melatonin 3 days before arrival at destination and 5 days after-flight) 2) **late melatonin group** (placebo for 3 days bedore arrival at destination and melatonin for 5 days after flight) 3)**placebo group**	Subjective VAS for jet lag, Sleepiness, Fatigue, Vigour, Activity	Statistically significant improvement in the group receiving melatonin only after flight (late melatonin)

Reference	Study type	Doses	N	Time zones	Direction	Time of administration	Endpoints	Conclusion
[redacted]	Double-blind, placebo-controlled crossover trial	5 mg	20	12	eastward	Pre-flight at 10-12:00 (local time) for 3 days, on flight day at 10-12:00 and for 3 days after flight at 22-24:00 (destination time).	Subjective VAS for jet lag, Sleepiness, Fatigue, Vigour, Activity, Daytime tiredness	VAS jet lag improved with melatonin compared to placebo
					westward			VAS jet lag was improved and sleep was re-established quicker with melatonin than placebo
	Double-blind, randomised placebo-controlled trial.	1) 5.0 mg melatonin at bedtime (n=64). 2) 0.5mg melatonin at bed time (n=70). 3) 0.5mg melatonin on an advancing schedule (n=63) 4) placebo (n=60)	257	6	eastward	Groups 1),2) and 4) on flight day and after flight at local bedtime for 5 days. Group 3) on flight day 11h after subjects's usual wake up time and for the next 5 days one hour earlier every evening.	Columbia Jet Lag Scale	Melatonin had no effect in alleviating jet lag sympotms compared to placebo
	Double-blind crossover design placebo-controlled. Jet lag simulation study inducing 9h phase advance in isolated facility	5 mg	8	9	eastward (need to phase advance)	Pre-flight (before inducing phase shift) at 18:00h (local time) for 3 days and at 14:00h after-flight (after inducing phase shift) for 4 days	Body temperature. Urine excretion of: corticosteroids, calcium, potassium, sodium. Performance tests. Sleep daily logs Subjective questionnaire for jet lag. Stanford Sleepiness Scale.	Melatonin hasted resynchronization versus placebo of the majority of variables measured.
	Double-blind, randomised, four-leg crossover; placebo-controlled study Jet lag simulation study in a controlled environment	1)5 mg melatonin + dim light 2)placebo + dim light, 3)5 mg melatonin + bright light 4)bright light + placebo	8	9	eastward (need to phase advance)	After flight (after inducing phase shift) at 23:00 for 3 days. Bright light at 0800-1200h for 2 days after phase shifting in groups 3) and 4)	Body temperature. Subjective behavioural measurements Urinary 6-Sulphatoxymelatonin	Melatonin improved re-synchronisation of body temperature, sleep, alertness and performance efficiancy, irrespectively of light
	Double-blind, randomised, placebo-controlled study with 3 groups	1)300 mg SR caffeine 2)5 mg melatonin 3)placebo	27 (9 per group)	7	eastward	Group 1) Caffeine was administered for 5 days after flight at 8:00 Group 2) Melatonin was administrered pre-flight at 17:00 on flight day at 16:00	Sleep, Daytime sleepiness, Oral temperature, Saliva melatonin, Saliva cortisol	Melatonin had beneficial effects on jet lag treatment mainly by improving sleep. Melatonin helped the resynchronisation of hormones

Reference	Study type	Doses	N	Time zones	Direction	Time of administration	Endpoints	Conclusion
[redacted]						and after arrival for 3 days at 23:00		
	Placebo-controlled double-blind	5 mg	31	10	eastward	On flight day 18:00-19:00 (local time) and after-flight for 4 days at 22:00-23:00 (destination time)	Grip strength and intra-aural temperature, Subjective VAS of jet lag. Subjective questionnaire	Melatonin did not show any difference from placebo
	Double blind, repeated measures, placebo controlled	3 trans-atlantic missions over which they took each of the 3 medications : placebo, 2mg melatonin SR, 7.5mg zopiclone	30	5	eastward	After arrival 17:00 body clock (22:00 local time) only once	Actigraphy, Sleep log diaries, Subjective questionnaire on sleep	Melatonin and Zopiclone improved sleep measures equally and both were better than placebo
	All the same protocol of melatonin, light and exercise. There was no placebo control.	3 mg	22	12	westward	On flight day at 11:00 and after flight for 6 days at 23:00 (destination time)	Sleep log diaries, Subjective questionnaire on sleep, Morning alertness, Actograms, urinary 6-Sulphatoxymelatonin	Melatonin resynchronised sleep and wakefulness in an average of 2,13 days significantly different from the 6 days expected after a 12-h shift
	All the same protocol of melatonin, light and exercise. There was no placebo control.	3 mg	75	13	eastward	On flight day melatonin at 10:00 (local time) after flight 30 min pre-bedtime for 7 days	Subjective VAS for jet lag, Sleep log diaries, Actograms based on sleep log diaries,	Melatonin resynchronised sleep and wakefulness in an average of 2,27 days faster than expected
			59	11	westward	Pre-flight for 7 days (as they were passengers form the eastward flight) pre-bedtime on flight day at 13:00 (local time) and after flight 30min pre-bedtime for 8 days		Melatonin resynchronised sleep and wakefulness in an average of 2,54 days faster than expected after 13h phase shift
	Within-subject placebo-controlled counter-balanced study	3 mg	12	a gradual advance 1 h/day)	11 hours before baseline sleep midpoint on the first treatment day and 1 h earlier each subsequent day for 3 days		Dim Light Melatonin Onset (DLMO) from saliva. Sleep, Subjective symptoms rating. Psychomotor Vigilance and Subjective Sleepiness	Melatonin produced significantly larger phase advances (1.3 ± 0.7 h) compared to placebo (0.7 ± 0.7 h)
	Double-blind placebo-controlled	0.5 mg	50	1 hour per day phase shifting for 3 days	Melatonin 5h before baseline bedtime on treatment day1 and an hour earlier each day for 3 days. Subjects received three		Dim Light Melatonin Onset (DLMO) from saliva. Actigraphy, Subjective symptoms from Columbia Jet	Melatonin helped phase advance. The average magnitude of

Reference	Study type	Doses	N	Time zones	Direction	Time of administration	Endpoints	Conclusion
	for melatonin.				different morning bright light exposure patterns		lag Scale and from Sanford Sleepiness Scale	phase shift was equal to 3mg
	No placebo group	5 mg	14	6	eastward westward	After-flight at 23:00 (destination time) time during the flight and the first evening	Subjective questionnaire on sleep and wake-up quality compared to previous experiences of transcontinental travel.	Melatonin was found to effectively improve symptoms of jet lag
	Double blind placebo controlled, between-subjects design with melatonin dose as independent variable.	1) placebo (n=12) 2)0.5 mg melatonin (n=9) 3)3.0 mg melatonin (n=11)	32	7	eastward (need to phase advance)	After flight (after inducing the phase shift) 30 min before bedtime for 4 days	Body temperature. Dim light melatonin onset (DLMO) from saliva samples. Actigraphy. Subjective ratings of sleep, sleepiness and mood	Melatonin significantly helped to induce a phase advance and helped resynchronisation compared to placebo
	Comparison with sampling 1 day prior and 1 day after melatonin dosing (Takahashi et al., 2001)	3 mg	8	11	eastward	After-flight on the second day at 20:00 local time for 3 days	Subjective symptoms according to the Stanford Sleepiness Scale (SSS). Subjective VAS for jet lag. Blood levels of melaonin	Melatonin promoted antidromic re-entrainment, accelerated the rate of re-entrainment by 15 min per day and alleviated the jet lag symptoms
	Comparison with sampling 1 day prior and 1 day after melatonin administration (Takahashi et al., 1999)	3 mg	6	8	eastward	After-flight on the second day at 23:00 local time for 3 days	Blood levels of melatonin	Melatonin significantly hastened re-synchronization. Re-entrainement without melatonin was 31min/day with melatonin 76 min/day.
	Placebo-controlled, 4-week within-subject crossover design	5 mg	9	Phase shifts indu-ced by bright light, mela-tonin, their combina-tion	Melatonin or placebo at 20:40 hr, with or without a subsequent 3 hr light pulse (5000 lux) from 21–24 hr.		Saliva melatonin levels. Dim light melatonin onset (DLMO)	Melatonin significantly induced a phase advance compared to placebo

After a first screening of the clinical studies identified, the main difficulties regarding the administration of melatonin in this indication reside in the posology, the dosing scheme, the duration of treatment and significant variability in jet lag related to the time zones changed, whether the travel is eastward or westward and other idiosyncratic characteristics. Another difficulty that this indication discloses is the lack of objective endpoints establishing its efficacy

in a specific dose regimen for a specific period. The majority of studies used a subjective VAS of jet lag to assess its treatment. Other subjective endpoints commonly used were daytime sleepiness, alertness, depression, fatigue, performance in work or sports etc. Only few studies used objective measures such as wrist actigraphy, cortisol levels, melatonin levels, sleep characteristics (onset, latency, quality) and body temperature. In order to elucidate these aspects and conclude in an overall assessment based on published studies, an effort was attempted by the Applicant to make a thorough analysis of the existing data in order to reach a potential conclusion on those issues. The Applicant at first consulted several review papers and as a second step has performed an analysis of the data gathered, as presented below.

The meta-analysis of [redacted], reviewing **efficacy and safety of exogenous melatonin in managing** secondary sleep disorders and sleep disorders accompanying sleep restriction, such as **jet lag and SWD,** concluded that melatonin does not have a significant clinical benefit. This may have been because the investigators mainly examined the effect of melatonin on SOL or sleep efficiency; however, the main mechanism of action of melatonin for jet lag is its action as a chronobiotic by helping resynchronisation of all circadian rhythms resulting in less daytime fatigue and ameliorating many aspects of all-day long routine. It has been proposed that the administration of 5 mg melatonin for the treatment of jet lag in athletes, especially during daytime, does not provide any clinical benefit in relation to athletic performance and sleep [redacted] However, the Cochrane meta-analysis [redacted] found that melatonin, taken close to the target bedtime at the destination (22:00 to midnight), decreased jet lag from flights crossing ≥5 time zones, by including 10 trials that met the inclusion criteria. Eight of the 10 trials found that melatonin, taken close to the target bedtime at the destination (22:00 to midnight), decreased jet-lag from flights crossing ≥5 time zones. Daily doses of melatonin between 0.5 and 5 mg are similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg. Doses above 5 mg appear to be no more effective. The relative ineffectiveness of 2 mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The estimated number-needed-to-treat (NNT) is 2, based on the only two trials that gave the necessary data. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time. The incidence of other side effects is low. The reviewers concluded that melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe. It should be recommended to adult travelers flying across ≥5 time zones, particularly in an easterly direction and especially if they have experienced jet lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be [redacted] combined 11 randomised trials, combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. It has been concluded that the use of oral melatonin reduces symptoms associated with jet lag syndrome.

A number of published review papers agree in the efficacy of 0.5-5.0 mg of melatonin in the treatment of jet lag in travelers [redacted] As already mentioned,

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

Basic Data Analysis of Clinical Studies presented in Table 17

In order to clearly define the actual outcomes of literature studies, the Applicant has performed a thorough analysis of clinical data. As in many studies both an eastward and a westward travel were performed, resulting many times in a different outcome, every travel was considered as being a different occasion and evaluated separately. Thus, it was found that, in 21 evaluable studies (i.e., excluding those studies simulating jet lag by inducing phase shifts), 28 travels were performed.

Elucidation of most implemented and efficient dose

Melatonin was proved beneficial in a total of 23 travels (15 eastwards and 8 westwards), found in a total of 17 studies. A total of 1,386 volunteers were included in these studies, of which 1,112 received melatonin and 437 received placebo. Doses used ranged from 0.5 mg to 10.0 mg with a mean (±SD) value of 4.5±1.9 mg (Figure 7). On the other hand, melatonin was found ineffective in the treatment of jet lag in a total of 5 travels (3 eastwards and 2 westwards), found in a total of 4 studies. A total of 348 volunteers were included in these studies, of which 260 received melatonin and 124 received placebo. Doses used ranged from 0.5-5.0 mg with a mean (±SD) value of 4.25±1.84 mg (Figure 7).

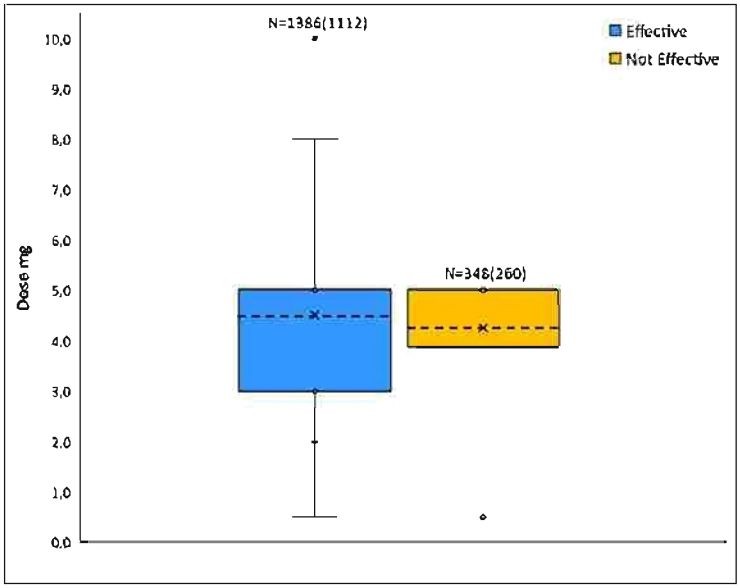

Figure 7. Box-Plot diagram, depicting the doses used in the studies investigating the efficacy of melatonin in jet lag.

Elucidation of dosing schedule and need of pre-treatment (Figure 8)

As evidenced by the studies evaluated, time of administration plays a crucial role for melatonin effects on circadian rhythms. Administration time is strongly related to the desired effects. For instance, daytime administration of 0.1-0.3 mg generated serum melatonin C_{max} within the normal nocturnal ranges of untreated people. These and higher doses produce measurable hypnotic effects independently of the circadian time signal synchronising action [redacted] The need of a well-designed administration scheme is also supported by the fact that the observed differences on melatonin effects in relation to administration time are not due to differences in PKs but to differences in the already existing melatonin concentration and in the phase of circadian human rhythm [redacted] Therefore, in order to find the optimum dosing scheme, an overall assessment of the studies identified was performed as described below.

Travels with pretreatment

In 10 travels, administration of 0.5-5.0 mg of melatonin (starting administration before flight) showed a positive outcome. Among them, 7 travels were eastwards and 3 were westwards, with a change of 8-13 time zones. From a total of 661 volunteers, 520 received melatonin and 160 took placebo [redacted]

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

In 3 travels, administration of 0.5-5.0 mg melatonin (starting administration before flight) showed a negative outcome. Two of these travels were eastwards and 1 was westwards with a change of 6-11 time zones. From a total of 312 patients, 224 received melatonin compared to 88 that received placebo [redacted]

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

Travels with treatment only after arrival

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

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

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

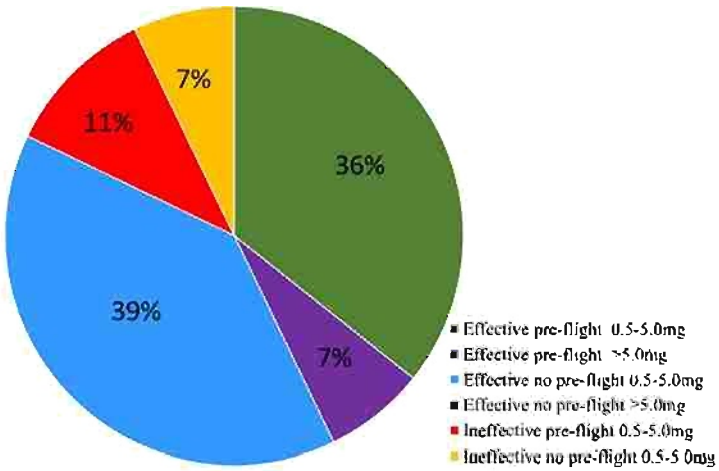

Figure 8. Pie chart depicting the efficacy of melatonin in relation to doses administered and pre-flight administration. Also, the % of the overall travels reviewed (28 travels in total) that belong to each category, is presented.

It seems evident that, the most effective applied schemes were 0.5-5.0 mg starting the administration pre-flight or starting the administration after arrival at destination. A further evaluation of doses administered in jet-lag clinical trials can be seen in Figure 9 below. Melatonin 3 mg and 5 mg were the most frequently administered effective doses in the clinical trials found in the literature.

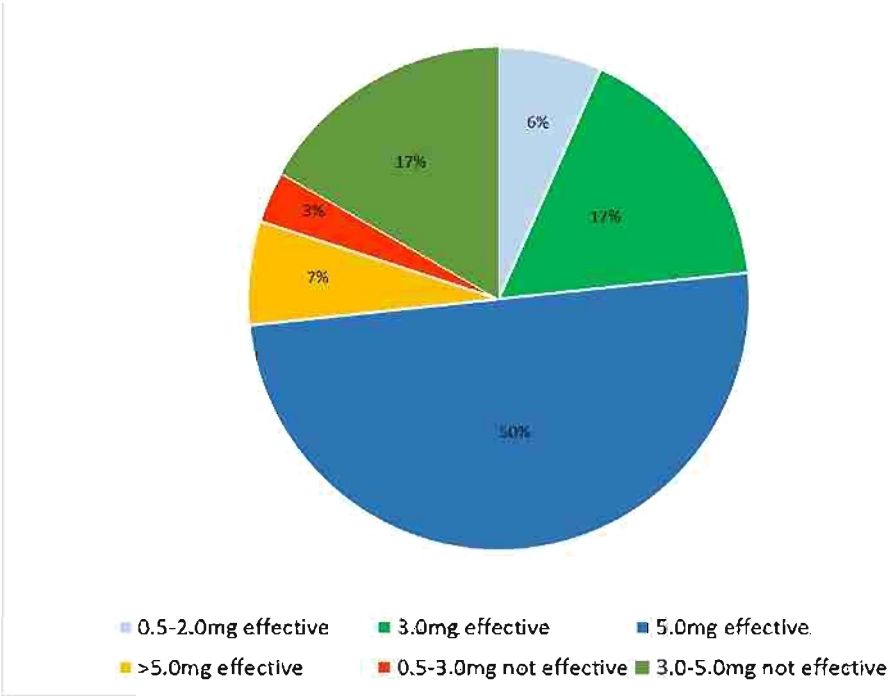

Figure 9. Pie chart depicting the efficacy of melatonin in relation to doses administered.

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

- A total of 973 volunteers were included in studies where 0.5-5.0 mg melatonin or placebo was administered starting pre-flight. Among them, the 53% receiving melatonin showed a positive outcome while the 23% receiving melatonin showed a negative outcome.
- A total of 808 volunteers were included in studies where 0.5-5.0 mg melatonin or placebo was administered starting the administration after arrival at destination. Among them, the 69% receiving melatonin showed a positive outcome while the 4.5% receiving melatonin showed a negative outcome.

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

only after flight showed alleviation from jet lag while the group receiving pre-flight melatonin showed a worse recovery compared to placebo.

This scheme and dosing is also in general agreement with the PKs of melatonin, suggesting a T_{max} at 30-50 min after administration [redacted] its PDs implying that melatonin receptors are saturated at levels above >200 pg/mL which is reached with a dose of >0.5 mg [redacted]

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

Efficacy studies simulating jet lag

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

A total of 6 studies investigating the efficacy of melatonin in inducing phase shifts towards a precise direction or in alleviating simulated jet lag in a controlled environment without the participation of volunteers in actual travels, were found and reviewed (Table 17). The main advantage of these tests was the fact that the endpoints used were mainly objective, such as DLMO from saliva sample, urine excretion of hormones and electrolytes and sleep characteristics (onset, latency, quality), in combination with subjective measurements as subjective questionnaires on performance, fatigue, alertness and mood. Another advantage of these studies was also the possibility of completely controlling the exposure to light as a result, to assess only the effects of melatonin in resynchronization. However, these studies do not take into account the normal travel fatigue, the average exposure to light during/after flight or other environmental factors but considers the effects only from change of time zone.

All the studies proved that melatonin hastens resynchronisation and ameliorates jet lag symptoms. The doses of melatonin used were 0.5 mg or 3.0 mg or 5.0 mg and all of them exerted similar efficacy. Two out of 6 studies evaluated the effects of a gradual phase advance of 1 h/day induce with the help of melatonin 0.5 mg or 3.0 mg in healthy volunteers [redacted] 2 out of 6 studies [redacted] started the administration of melatonin after the simulation of the travel, i.e. after inducing in volunteers 7-9 h change of time zone in a controlled environment, 1 out of 6 studies started the administration of melatonin before the simulation of the travel, i.e. 3 days before inducing in volunteers 9 h change of time zone in a controlled environment [redacted], 1 study investigated the phase shifts that produced by 5 mg melatonin, with or without light exposure after administration in the late evening [redacted] (Table 17).

In conclusion, also from these studies, the dosing scheme of 3.0-5.0 mg melatonin administered 30-60 min in the new time zone seems to be effective.

Overall efficacy conclusions

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

Although two of the reviewed studies were negative (see Table 17), the evidence is overall quite supportive that melatonin, administered at appropriate time, may reduce the symptoms of jet lag and improve sleep following travel across multiple time zones. Based on the published literature, efficacy of melatonin treatment for jet lag seems moderately convincing provided that a specified dosing schedule is followed, i.e., if it is taken close to the target bedtime at the destination; however, a harmonised approach regarding dosing recommendation is not achieved in the literature; the best clinical practice is not yet clear cut. The large variability of dosing schemes and doses proposed are noticed. The dose range used in the studies was 0.5 mg to 10 mg and the vast majority indicated a favourable effect on jet-lag in adults; most of the studies investigated a dose of 5 mg. IR formulations in doses of 0.5-5 mg appear generally effective. However, results of studies with low dose of melatonin (i.e., 0.5 mg and 2 mg in the study by [redacted] suggest that such very low doses are not always effective. Not forgetting also that, observations from a dose-effect relationship demonstrated with melatonin in artificially induced acrophase shift [redacted] agree with results from [redacted] suggesting that pharmacological doses of melatonin (5 mg) induce larger advances of the endogenous melatonin rhythm and therefore faster resynchronization of the sleep-wake cycle than physiological doses (0.5 mg). Furthermore, doses above 5 mg (and up to 10 mg) have been administered in the published jet-lag trials (Table 17), being effective as well as safe. In any case, it is suggested to prefer the administration of the lower pharmacololgical doses of melatonin in order to both allow its chronobiotic effect to be manifested and limit its hypnotic effect [redacted] This observation is in agreement with findings of studies related to PKs and PDs (as described in the corresponding Section of the current Clinical Overview). Indeed, also in the Cochrane Review of [redacted] it is concluded that doses between 0.5 mg and 5 mg appear to be similarly effective, apart from the greater hypnotic effect of higher doses. For many people, 5 mg may be a higher dose than necessary: 2 or 3 mg may therefore be preferable to start with and, in any case, a dose of 6 mg could be regarded as the highest recommended daily dose in case such is needed. There seems to be no reason to think that efficacy may be decreased with higher doses above 3-5 mg, since there is no such evidence of e.g., a bell-shaped dose-response curve.

It should also be noted that IR dosage forms are more efficient than SR for jet lag treatment [redacted]

Taking all the above studies and reviews into consideration, it may be concluded that the potentially best dosing scheme for **eastward and maybe for westward flights, crossing more than 5 time zones, is 0.5-5.0 mg (most proposed: 2-3 mg) of IR melatonin, 30-60 min before bedtime at the destination time zone, starting on travel day and continuing for 3-5 days after arrival at destination until resynchronisation, based on subjective indices of jet lag.** Therefore, recommending 3 mg starting dose with a possibility to increase to 6 mg, as in the

proposed posology, may be considered as supported by the evidence. This scheme of dosing (i.e., up to 6 mg as maximum daily dose) is proposed in order to be in general agreement with the PKs of melatonin and the SmPCs of the already marketed IR melatonin (oral solid and liquid) products in EU/UK with jet lag as indication; in this way, consistency between potentially interchangeable solid and liquid products in the management of jet lag in adults can be achieved.

2.5.4.2 SLEEP DISORDERS IN CHILDREN AND ADOLESCENTS AGED 6-17 YEARS WITH ADHD, WHERE SLEEP HYGIENE MEASURES HAVE BEEN INSUFFICIENT

Sleep disturbances are highly prevalent in children and without appropriate treatment, they can become chronic and last for many years; however, distinguishing sleep disturbances from normal age-related changes can be a challenge for physicians and may delay treatment. ADHD is a disorder that encompasses symptoms of inattention, hyperactivity and impulsivity. Beginning around puberty, people with ADHD are more likely to experience shorter sleep time, problems falling asleep and staying asleep as well as a heightened risk of developing a sleep disorder. Sleep problems in ADHD tend to increase with age, though sleep problems in early childhood are a risk factor for future occurrence of ADHD symptoms. Sleep problems in ADHD appear to differ depending on the type of the disorder; individuals with predominantly inattentive symptoms are more likely to have a later bedtime, while those with predominantly hyperactive-impulsive symptoms are more likely to suffer from insomnia. Those with combined hyperactive-impulsive and inattentive ADHD experience both poor sleep quality and a later bedtime [redacted]

Some published studies have shown that melatonin can be safe and effective not only in the case of primary sleep disorders, but also for sleep disorders associated with various neurological conditions [redacted] Melatonin decreases SOL and increases total sleep time but does not decrease night awakenings. However, there is generally still uncertainty concerning dosing regimens. Decreased CYP1A2 activity, either genetically determined or due to concomitant medication, can slow metabolism, with loss of variation in melatonin level and loss of effect; decreasing the dose can remedy this [redacted] The dose of melatonin should, therefore, be individualised on the basis of multiple factors, including the severity and type of sleep problem and the associated neurological pathology [redacted]

A thorough literature investigation has been performed and article selection was based on the general principles of PRISMA checklist. A schematic representation of the relevant selection flowchart for the use of melatonin in sleep disorders in paediatric ADHD is provided below.

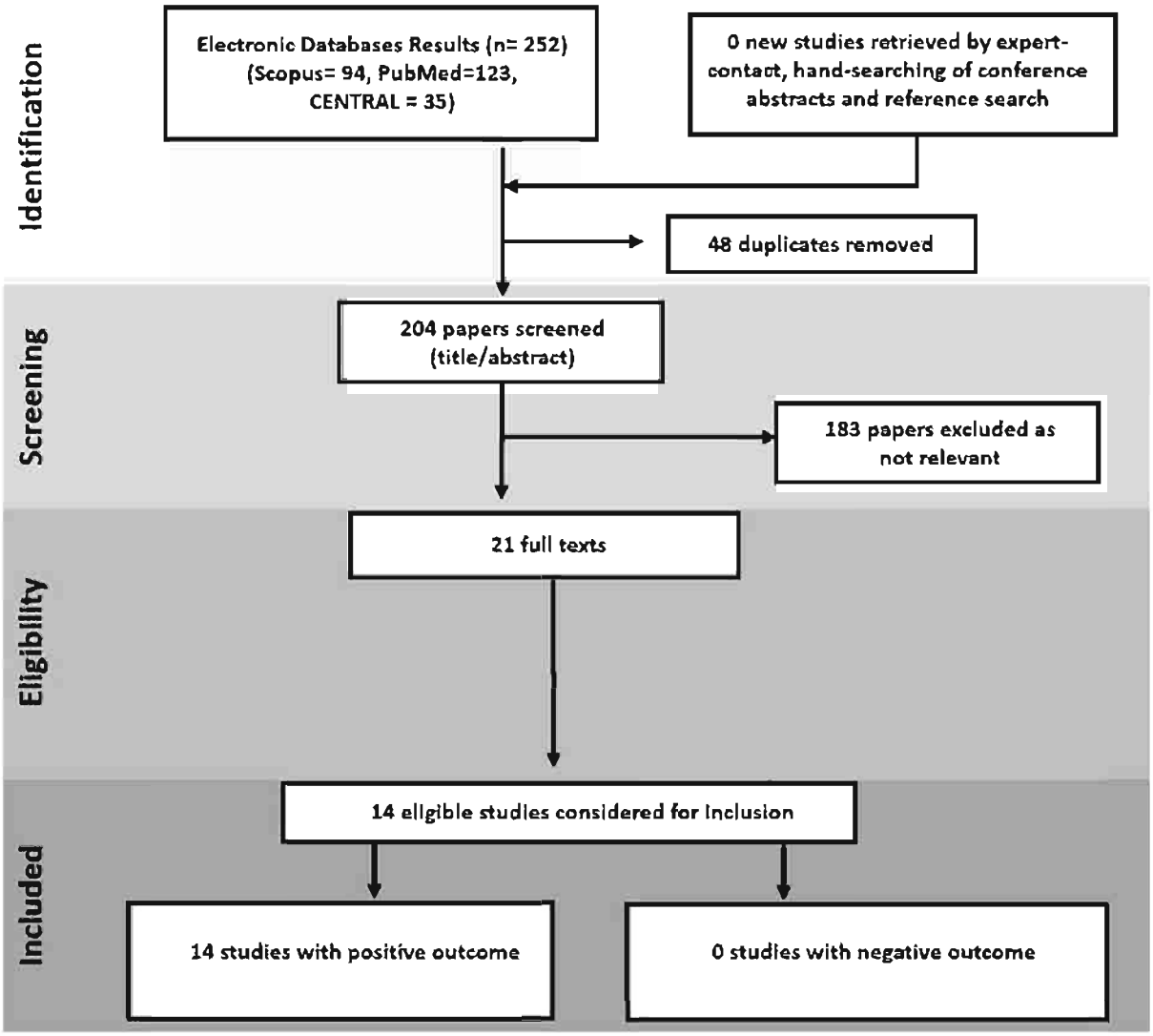

Figure 10. Flowchart for selection of articles based on PRISMA general principles for the use of melatonin in sleep disorders in paediatric ADHD.

Table 18 summarises the methods, population groups, regimens and efficacy/safety outcomes of 14 clinical studies involving oral melatonin administration for the management of sleep disturbances in children with ADHD (among others) [redacted] and 1 randomised, double-blinded, placebo-controlled, parallel trial with 146 children with neurodevelopmental problems aged from 3 years to 15 years 8 months who had sleep disorders (without specifying the type of the disorders) [redacted] Of the 14 studies, 9 were randomised placebo-controlled trials [redacted] 1 was open-label pilot study [redacted]

[redacted] 1 was retrospective trial [redacted], 2 were (prospective) observational naturalistic studies [redacted] and 1 was collaborative, uncontrolled, open-label, phase III trial [redacted] The studies cover a chronological period from 2001 to 2020 with more than 900 children and adolescents, aged from 6 to 17.5 years, thus covering the target group of the proposed indication, from whom 601 had ADHD (either on treatment with MPH or not), with the children receiving melatonin supplementation being slightly more than the 50% of the total study population. The examined administered oral doses of melatonin cover a range of 1 to 10 mg before pedtime, usually in the form of tablets [redacted] capsules, which were supplements, [redacted] or granules [redacted]. Doses of 3-6 mg (given before the designated bedtime) were most frequently administered among paediatric patients (Table 18), which is in accordance with the recommended posologies in the currently proposed SmPC for this indication and target population group. The investigated endpoints included sleep latency, sleep onset, total night sleep time, sleep duration, wake-up time, DLMO, mean number of awakenings, mean longest sleep episode and sleep patterns among others. Overall, a positive effect of melatonin supplementation in sleep outcome of paediatric patients with ADHD is reported in all identified clinical trials, indicating a well acknowledged, favourable efficacy profile of the agent in the specific indication.

Table 18. Clinical studies identified in the literature investigating the efficacy of oral melatonin administration for the treatment of sleep disorders in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. ***Keynote:*** *Red colour denotes lack of effect, yellow colour denotes moderate effects, green colour denotes favourable efficacy results.*

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
Melatonin for sleep disorders in children with ADHD							
[redacted]	Randomised, double-blind, placebo-controlled study (the Netherlands)	To investigate the effect of melatonin treatment in childhood sleep onset insomnia.	Primary: between-group differences in the mean change from baseline to week 4 for: lights-off time, SL, sleep onset, sleep duration, wake-up time, DLMO, reaction times and number of omissions, corrections and errors.	4 weeks (after that period, treatment was continued if parents wished so)	40 elementary school children, aged 6-12 years, who suffered more than 1 year from chronic sleep onset insomnia (from them 11 boys had ADHD and received MPH medication)	Either 5 mg **melatonin or placebo (in a fast-release tablet), at 18:00**	Melatonin: mean (95% CI) lights-off time advanced was 34 (6-63) min; diary sleep onset 63 (32-94) min, actigraphic sleep onset 75 (36-114) min; melatonin onset 57 (24-89) min; TST increased 41 (19-62) min. Placebo: these parameters did not shift significantly. The change during the 4-week treatment period differed between treatment groups significantly as to lights-off time, diary and actigraphic sleep onset, sleep duration and melatonin onset. No significant differences between the treatment groups in the change of SL, wake-up time and sustained attention reaction times.
	Preliminary open-label pilot study	To investigate whether melatonin	-	Up to 12 weeks	27 children with sleep disorders who	3 mg **melatonin** (time of	24 subjects completed the study with short-term use (1-4 weeks). The results of

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
	(the Netherlands)	could be used as a safe drug to treat insomnia problems in children with ADHD on MPH medication.			also had ADHD on MPH use	supplementation and type of formulation not stated)	the long-term effects are only available from 13 of 24 subjects. Immediately after initiation of melatonin treatment, the subjects fell asleep significantly earlier than before, time varying between 15 to 240 min (median: 135 min). The long-term effect (after 3 months) was comparable with the immediate effect after 1 week. A paired student t-test for the time of falling asleep before and after medication proved to be significant (t=16.05, P<0.01). The time of falling asleep after melatonin varied between 15 and 64 min. Comparing the long-term effect to the immediate effect showed that melatonin remains for at least 3 months. No statistical difference could be shown in short-term effect of melatonin between those who stopped recording data and those who did not (P<0.50).
	Randomised, double-blind, placebo-controlled trial (the Netherlands)	To investigate the effect of melatonin treatment on health status and sleep in children with idiopathic sleep-onset insomnia.	Primary: the between-group differences in change on the FS-II and RAND-GHRI from baseline to week 4. Secondary: sleep log lights off time, SL, sleep onset, sleep duration, wake-up time and DLMO.	4 weeks	62 children (28 had ADHD. 22% in the melatonin and 54% in the placebo group) aged 6-12 years who suffered >1 year from idiopathic chronic sleep-onset insomnia	Either 5 mg **melatonin** (Duchefa Farma BV, the Netherlands) or placebo (in a **fast-release tablet**) at **19:00**	The total scores of the RAND-GHRI and FS-II improved significantly more during melatonin treatment than placebo. The magnitude of change was much higher in the melatonin than placebo group, with standardised response means for the RAND-GHRI of 0.69 vs 0.07 and for the FS-II of 1.61 vs 0.64. Melatonin treatment also significantly advanced sleep onset by 57 min, sleep offset by 9 min and melatonin onset by 82 min and decreased SL by 17 min. Lights-off time and TST did not change.
	Retrospective study (Israel)	To describe the effects of long-term treatment with melatonin in adolescents with delayed sleep phase syndrome.	Subjective sleep onset time and sleep duration.	6 months (12 patients, i.e., 36%, were treated for >6 months; 5 of them were treated for ≥1 year)	33 adolescents (aged 10-18 years) with delayed sleep phase syndrome and comorbid neurodevelop mental disorders, including 15	**Oral melatonin 3-5 mg/day, given ~2 h before designated bedtime**, for an average period of 6 months (type of formulation or product not stated)	During treatment, the sleep onset was advanced and sleep duration was longer. Treatment was also associated with a decrease in the proportion of patients reporting school difficulties. No AEs of melatonin were noted.

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
					children with ADHD		
	30-Day, randomised double-blind, placebo-controlled, crossover trial (Canada)	To evaluate the efficacy of sleep hygiene and melatonin treatment for initial insomnia in children with ADHD who were treated with stimulants.	Primary: mean SOL. Secondary: night-to-night variability in SOL given by the standard deviation of SOL and total sleep duration.	10 days	27 stimulant-treated children (aged 6-14 years; mean: 10.29 years) with ADHD and initial insomnia (>60 min) who received sleep hygiene intervention, 19 were non responders were used in the study intervention	Short-acting pharmaceutical-grade melatonin (provided by the sponsor of the study Circa Dia BV; type of formulation not stated), 5 mg given 20 min before bedtime.	Sleep hygiene reduced initial insomnia to <60 min in 5 cases, with an overall effect size in the group as a whole of 0.67. Analysis of the trial data able to be evaluated showed a significant reduction in initial insomnia of 16 min with melatonin relative to placebo, with an effect size of 0.6. The effect size of the combined sleep hygiene and melatonin intervention from baseline to 90 days post-trial was 1.7, with a mean decrease in initial insomnia of 60 min. Improved sleep had no demonstrable effect on ADHD symptoms.
	Randomised, double-blind, placebo-controlled study (the Netherlands)	To investigate the effect of melatonin treatment on sleep, behaviour, cognition and quality of life in children with ADHD sleep-onset insomnia.	Primary: actigraphy-derived sleep onset, total time asleep and salivary DLMO.	4 weeks	105 paediatric patients (aged 6-12 years) with diagnosed ADHD and sleep-onset insomnia	**Melatonin 3 mg when body weight <40 kg (n=44); 6 mg when body weight >40 kg (n=9)** or placebo (**fast-release tablets, Pharma Nord, Denmark**) at **19:00**	Sleep onset advanced by 26,9±47.8 min with melatonin and delayed by 10.5±37.4 min with placebo (P<0.0001). There was an advance in DLMO of 44.4±67.9 min in melatonin and a delay of 12.8±60.0 min in placebo (P<0.0001). Total time asleep increased with melatonin (19.8±61.9 min) over placebo (-13.6±50.6 min; P=0.01). There was no significant effect on behaviour, cognition and quality of life.
	Long-term follow-up study in children that previously participated in the randomised, double-blind, placebo-controlled trial of Van der Heijden et al. (2007) (the Netherlands)	To assess long-term melatonin treatment course, effectiveness and safety in children with ADHD and chronic sleep onset insomnia.	Melatonin use and current dose, time of administration, the reasons for discontinuation of melatonin, temporary discontinuation, effects of discontinuation on sleep and behaviour, adverse events, unusual comorbidity during treatment; effects of melatonin on sleep onset problems, behaviour and mood	Mean follow-up: 3.66±0.12 years	94 children with ADHD (74.5% were male; mean ± SEM age at start of melatonin treatment: 8.72 ± 0.21 years and mean ± SEM age at follow up: 12.39 ± 0.25 years)	**3-6 mg melatonin at 18:30-23:00** (type of dosage form not specified)	65% of the children still used melatonin daily and 12% occasionally. Temporal discontinuation of treatment resulted in a delay of sleep onset in 92% of the children. A 9% of the children could discontinue melatonin completely due to improvement of sleep onset insomnia. Long-term treatment was judged to be effective against sleep onset problems in 88% of the cases. Improvement of behaviour and mood was reported in 71% and 61%, respectively.
	Randomised, double-blind, placebo-	To determine melatonin effects	ADHD rating scale and	8 weeks	50 children (aged 7-12 years; mean	Either **melatonin 3 or 6 mg**	The mean SL and total sleep disturbance scores were reduced in the melatonin

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
[redacted]	controlled study (Iran)	on sleep patterns, symptoms of hyperactivity and attention deficiency in children with ADHD.	SDSC sleep questionnaires were completed by mothers at baseline, 2, 4, and 8 weeks after beginning of the treatment.		age in the melatonin group: 9.57±1.65 years and 8.83±1.82 years in the placebo group) who had a combined form of ADHD	**(capsules, Nutricenturl, Canada)** (i.e., 3 mg when body weight <30 kg and 6 mg when >30 kg) combined with MPH (1 mg/kg) (n=26), or placebo combined with MPH (1 mg/kg) (n=24). Time of supplementati on not stated.	group, but they increased in the placebo group ($P \geq 0.05$). Data analysis (using ANOVA with repeated measures) did not show any statistically significant differences between the two groups in ADHD scores (namely reduction of attention deficiency and hyperactivity behaviour of children with ADHD).
	Randomised, double-blind, placebo-controlled study (Iran)	To evaluate melatonin supplementati on effects on dietary intake, growth and development of children with ADHD treated with MPH through circadian cycle modification and appetite mechanisms.	3-day food record and standard weight and height of children were evaluated prior to the treatment and 8 weeks after the treatment.	8 weeks	50 children aged 7-12 years who were newly diagnosed with a combined form of ADHD (mean age: 9.57 ± 1.65 years in the melatonin and 8.83 ± 1.82 years in the placebo group)	Either **melatonin 3 or 6 mg (3-mg capsules, Nutricentury, Canada)** (i.e., 3 mg when body weight <30 kg and 6 mg when >30 kg) combined with MPH (1 mg/kg) (n=26), or placebo combined with MPH (1 mg/kg) (n=24). Time of supplementati on not stated.	Paired sample t-test showed significant changes in SL (23.15±15.25 vs 17.96±11.66: P=0.047) and total sleep disturbance score (48.84±13.42 vs 41.30±9.67: P=0.000) before and after melatonin, respectively. Appetite and food intake did not change significantly during the study. Sleep duration and appetite were significantly correlated in melatonin group (Pearson r=0.971, P=0.029). Mean height (138.28±16.24 vs 141.35± 16.78; P=0.000) and weight (36.73±17.82 vs 38.97±17.93; P=0.005) significantly increased in melatonin-treated children before and after the trial.
	11-Month, prospective observational naturalistic study (United Kingdom)	To assess the effects of melatonin on sleep onset delay, TST and night awakenings in children with ADHD, autism spectrum disorders or intellectual disability using a broad dose range.	Sleep patterns	11 months (326 days)	45 children (35 males, mean age: 6.3±1.7 years) with neurodevelop mental disorders (n=29: intellectual disability; n=9: autism spectrum disorder; n=7: ADHD) and sleep disturbances	**Melatonin IR oral form** (formulation not stated) was initially administered at a **starting dose of 2.5 mg, 30 min before** the desired **bedtime**, regardless of age or weight. If no significant improvement in sleep after 4 weeks, **dose was increased up to 5 mg** and after a	38% of children responded to low (2.5-3 mg), 31% to medium (5-6 mg) and 9% to high doses (9-10 mg) of melatonin, with a significant increase in night TST, decreased sleep onset delay and decreased number of awakenings per night (all: P=0.001), as measured with sleep diaries. No serious AEs were reported

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
						further 4 weeks to a maximum of 10 mg if no response to 5 mg was seen.	
	Multicentre (including the United Kingdom), randomised, double-blind, placebo-controlled trial	To assess the efficacy and safety of a novel PedPRM vs placebo for insomnia in children and adolescents with autism spectrum disorder, with or without ADHD comorbidity, and neurogenetic disorders.	Primary: the changes from baseline in mean TST over the 14 days. Secondary: the change from baseline in mean SL, the changes from baseline in mean duration of wake after sleep onset, mean number of awakenings and mean longest sleep episode, change from baseline in CSDI score and subscores, and number of dropouts during study.	2.2 years	A total of 125 children and adolescents (aged 2-17.5 years) with autism spectrum disorder whose sleep failed to improve on behavioural intervention alone; 28.8% of them had ADHD (n=36)	**PedPRM (2 mg escalated to 5 mg; pediatric-appropriate prolonged-release melatonin minitablets, Neurim Pharmaceuticals)** or placebo for 13 weeks.	The study met the primary endpoint: after 13 weeks of double-blind treatment, participants slept on average 57.5 min longer at night with PedPRM compared to 9.14 min with placebo (adjusted mean treatment difference PedPRM-placebo -32.43 minutes; P=0.034). SL decreased by 39.6 min on average with PedPRM and 12.5 min with placebo (adjusted mean treatment difference -25.30 min; P=0.011) without causing earlier wakeup time. The rate of participants attaining clinically meaningful responses in TST and/or SL was significantly higher with PedPRM than with placebo (68.9% vs 39.3%, respectively; P=0.001) corresponding to a NNT of 3.38. Overall CSDI tended to decrease.
	Randomised placebo-controlled trial (ouble-blind for melatonin/ placebo) (the Netherlands)	To compare the effects of melatonin and bright light treatment with a placebo condition in children with chronic sleep onset insomnia and late melatonin onset.	Questionnaire on chronic sleep reduction and DLMO measurements.	3-4 weeks	84 children (mean age: 10.0 years; 61% boys), in particular, 6, 5 and 8 children from the placebo, melatonin and light group, respectively, had ADHD	Placebo, **melatonin 3 mg (3 mg, fast release tablets, Pharma Nord) at 19:00** (i.e., ~2 h before DLMO) or light exposure during 30 min between 06:00 and 08:00 h.	Melatonin treatment and light therapy decreased SL (sleep diary) and advanced sleep onset (sleep diary and actigraphy), although for sleep onset the effects of melatonin were stronger. Melatonin treatment also advanced DLMO and had positive effects on SL and sleep efficiency (actigraphy data) as well as sleep time (sleep diary and actigraphy data). However, wake after sleep onset (actigraphy) increased with melatonin. No effects on chronic sleep reduction were found.
	Observational naturalistic Study (Italy)	To explore the effectiveness of melatonin in children with ADHD who developed sleep problems after starting MPH.	Severity of the sleep disorder at baseline (CGI-I, CGI-S), assessment of sleep problems.	Treatment duration of 4 weeks, with a maximum of 12 months, based on clinical outcomes.	74 children (69 males; mean age: 11.6±2.2 years) naturalistically treated with MPH (mean dosage: 33.5±13.5 mg/day)	**Melatonin 1-5 mg (dosage form not stated; starting dose was 1 mg after dinner, around 20:00-21:00, ~1-2 h before bedtime),** with possible increases of	Clinical severity of sleep disorders was 3.41±0.70 at baseline and 2.13±1.05 after follow-up (P<0.001). According to CGI-I score, 45 patients (60.8%) responded to melatonin treatment. Gender and age (children aged <12 and >12 years) did not affect the response to melatonin on sleep. Patients with/without

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
						0.5 mg every week, up to 5 mg/day, according to clinical needs (mean dosage: 1.85±0.84 mg/day)	comorbidities did not differ according to sleep response. Specific comorbidities with disruptive behaviour and affective disorders and learning disabilities did not affect the efficacy of melatonin on sleep. Treatment was well tolerated; no AEs related to melatonin were reported.
	26-Week, multicentre, collaborative, uncontrolled, open-label, phase III clinical trial (Japan; Sponsor of the study: Nobelpharma Co., Ltd)	To long-term efficacy and safety of melatonin treatment for sleep problems in children with neurodevelop mental disorders who underwent adequate sleep hygiene interventions.	Primary: SOL in the medication phase I. Secondary: time from the onset of medication to medication suspension; SOL at the time of medication suspension; time from medication suspension to medication resumption; number of awakenings after sleep onset, time of falling asleep, wakening and awakening time, refusal to going to bed at prespecified bedtime, temper upon wakening, sleepiness intensity after awakening; and ABC-J.	The study consisted of the 2-week screening phase, the 26-week medication phases I and II, and the 2-week follow-up phase.	99 children (80 males and 19 females; aged 6-15 years and mean age: 10.4 years) with neurodevelop mental disorders, including 60 children with ADHD, long with sleep problems and aberrant behaviours	Children received 1, 2, or 4 mg melatonin granules (consisting of synthesised melatonin and of mannitol as the excipient; Nobelpharma Co., Ltd) orally in the medication phases, once daily before bedtime, starting at 1 mg per day.	Fifteen children received the maximal dose of 4 mg among the prespecified dose levels. SOL recorded with the electronic sleep diary shortened significantly (namely, mean±SD: -36.7±46.1 min; 95% CI: - 45.9 to - 27.5; $P<0.0001$) in the medication phase I from baseline. The SOL shortening effect of melatonin persisted in the medication phase II and the follow-up phase. Temper upon wakening and sleepiness after awakening improved significantly ($P<0.0001$ each) in the medication phase I from baseline and persisted in follow-up. The following subscales of the ABC-J improved significantly: stereotypic behaviour ($P=0.0322$) in medication phase I and irritability, hyperactivity and inappropriate speech ($P<0.0001$) in medication phase II.
	Melatonin in neurodevelopmental disorders as supportive data						
	Randomised, double-blind, placebo-controlled, parallel study (United Kingdom)	To determine whether or not IR melatonin is beneficial over placebo in improving total duration of night-time sleep in children with neurodevelop mental problems.	Primary: night TST (sleep diaries). Secondary: TST calculated using actigraphy data, SOL, sleep efficiency, Composite Sleep Disturbance Index score, global measure of child's sleep quality, Family Impact Module of the Pediatric Quality of Life Inventory, the	12 weeks	146 children with neurodevelop mental problems aged from 3 years to 15 years 8 months who did not fall asleep within 1 h of lights out or who had <6 h of continuous sleep (who completed the 4- to 6-week behaviour	**Melatonin capsules (Alliance Pharmaceuticals)** or placebo capsules in doses of **0.5 mg, 2 mg, 6 mg and 12 mg** for a period of 12 weeks (starting dose: 0.5 mg and could be escalated through 2 mg and 6 mg to 12 mg during	110 of the 146 children (75%) contributed data for the primary outcome. The difference in TST time between the melatonin and placebo groups adjusted for baseline was 22.43 min (95% CI: 0.52-44.34 min; $P=0.04$) measured using sleep diaries. A reduction in SOL, adjusted for baseline, was seen for melatonin vs placebo when measured by sleep diaries (-37.49 min, 95% CI -55.27 to -19.71 min; $P<0.0001$) and actigraphy (-45.34 min, 95% CI -68.75 to -21.93 min; $P=0.0003$). There were

Reference	Design	Objective (s)	Efficacy endpoints	Duration of melatonin use	Study sample (number of subjects, condition)	Dosing regimen	Efficacy results
[redacted]			Epworth Sleepiness Scale, number and severity of seizures, AEs.		therapy period)	the first 4 weeks, at the end of which the child was maintained on that dose).	no significant differences between groups in terms of the reporting of AEs. The results of other secondary outcomes favoured melatonin (but not statistically significant).

Abbreviations: ABC-J, aberrant behaviour checklist–Japanese version; ADHD, Attention Deficit Hyperactivity Disorder; AE, adverse event; ANOVA, Analysis of Variance; CI, confidence interval; CSDI, Composite Sleep Disturbance Index; DLMO, dim light melatonin onset; FS-II, Functional Status II; CGI-I, Clinical Global Impression Improvement; CGI-S, Clinical Global Impression Severity; IR, immediate release; MPH, methylphenidate; NNT, number needed to treatPedPRM, paediatric-appropriate, prolonged-release melatonin minitablets; RAND-GHRI, RAND General Health Rating Index; SD, standard deviation; SDSC, Sleep Disturbance Scale for Children; SEM, standard error of the mean; SL, sleep latency; SOL sleep onset latency; TEAEs, treatment-emergent adverse effects; TST, total sleep time.

A systematic literature review of 4 clinical trials [redacted] conducted by [redacted] included paediatric (aged 6-14 years) patients with ADHD also suffering from chronic sleep-onset insomnia who were administered melatonin at initial doses ranging from 3 to 6 mg, within a few hours prior to a scheduled bedtime (treatment duration recommended to be as short as possible). Most studies have shown improvements in sleep onset (about 0.5-2 h), sleep duration (approximately 0.33-1 h) and sleep latency (~20 min), while AEs were infrequent and mild, e.g., transient headaches and dizziness.

A subsequent clinical evaluation of assessment and management of sleep problems in youths with ADHD recommended that if behavioural strategies are not effective due to comorbid psychiatric disorders or ADHD medications, a pharmacological treatment may be considered for sleep onset difficulties [redacted]. In an effort to evaluate nutritional supplements for the treatment of ADHD, Bloch and Mulqueen suggested that melatonin appears to be effective in treating chronic insomnia in children with ADHD but appears to have minimal effects in reducing core ADHD symptoms. In any case, melatonin should be prescribed in a single, night-time dose of 3-6 mg (depending on child's body weight) and given approximately 30 min before bedtime [redacted]

The above were also confirmed by Bruni and colleagues concluding that melatonin given at doses ranging from 3 to 6 mg/night significantly reduced sleep onset delay and increased total sleep duration but did not impact on daytime ADHD core symptoms as might have been expected, considering that better sleep quantity/quality has been related to improvement in cognitive and behavioural functioning. This last finding might be accounted for by the short duration of most of the reviewed trials that was below 3 months, with limited data available for long-term treatment. In these studies, melatonin was generally well-tolerated both in the short- and long-term treatment duration. Most of the participants who discontinued treatment did so because sleep problems were no longer a major issue rather than due to intolerable treatment effects [redacted]

Long-term efficacy and safety of melatonin was evaluated by [redacted] who conducted an observational, naturalistic study in children with ADHD treated with methylphenidate supplemented with melatonin of 1-5 mg which lasted until 12 months. [redacted] also examined the effect of 3-6 mg melatonin supplementation in

medication-free children with ADHD with a mean time of follow up the 3.7 years. An improvement in patient behaviour was described and probably these differences may be related to the duration of therapy [redacted]. Although these studies present some limitations, it may be concluded that melatonin may remain an effective therapy also in the long-term for the treatment of sleep disorders in children with ADHD and has no safety concerns regarding serious AEs or treatment related co-morbidity.

In conclusion, **the available clinical studies demonstrated the effectiveness and safety of melatonin at doses of 1-6 mg before bedtime to phase shift the circadian system and improve sleep disturbances of paediatric patients with ADHD, by decreasing sleep latency and increasing the total sleep time.** The well-established use of the active substance in the specific indication has been well-justified through an adequate number of published studies identified in the scientific literature, covering a time period of 20 years of clinical use i.e., from 2001 to 2020, and with almost a thousand children and adolescents being exposed to oral melatonin with favorable therapeutic outcomes and acceptable safety. The widespread use of melatonin in sleep disturbances of paediatric ADHD in different territories around the world is also evident in the published clinical studies, with many of them being conducted within the European territory (Italy, the Netherlands, UK), but also in non-European countries, such as Canada, Iran, Israel and Japan. Overall, a positive effect of melatonin supplementation in sleep outcome of paediatric patients with ADHD is reported in all identified clinical trials, indicating a well acknowledged, favourable efficacy profile of the agent in the specific indication.

The number and the severity of side effects were found to be similar between children given placebo and those given melatonin in the available studies. The most common side effects reported in those given melatonin in the larger clinical studies were headache, hyperactivity, dizziness and abdominal pain. Based on these studies, melatonin appears to be safe in the short-term setting (e.g., use up to 4 weeks), whereas existing data also demonstrate a favourable long-term efficacy and safety profile of melatonin in children and young people with ADHD (please refer to Safety sections of this Clinical Overview). Besides, a liquid formulation, as the current product under development, is the best option for treatment of paediatric patients and is regarded as an appropriate, age-friendly formulation, based also on the evaluation of excipients' safety. Although some of the published trials have utilised solid formulations, it has to be taken into consideration that the bioavailability of the liquid forms is comparable to those of the IR solid forms (please refer to the Pharmacokinetics Section of the current Clinical Overview), with the PK parameters being within the range and approaching the mean of those obtained with the solid dosage forms; therefore, bridging is successfully met.

Last but not least, other similar melatonin oral solutions have been already approved in the EU/UK over the last 4 years (2019-2022), for the management of sleep disturbances in paediatric patients with ADHD, following WEU procedures [redacted] further justifying the applicability of the selected legal basis for the submission of the currently developed product.

2.5.4.3 SHIFT-WORK DISORDER (SWD)

In order to elaborate the WEU on melatonin for the management of SWD in adults based on the publicly available data, a thorough literature review was performed, aiming to properly describe the relevant aspects regarding the efficacy and safety of the active substance. Therefore, after a detailed evaluation of the literature, published data were assessed in order to elucidate the time over which melatotin has been in use for the SWD in adults, the doses implemented, the degree of scientific interest in the use of the active substance and the coherence of scientific evaluations. Figure 11 depicts the search strategy and article selection methodology followed which was based on the general principles of the PRISMA checklist.

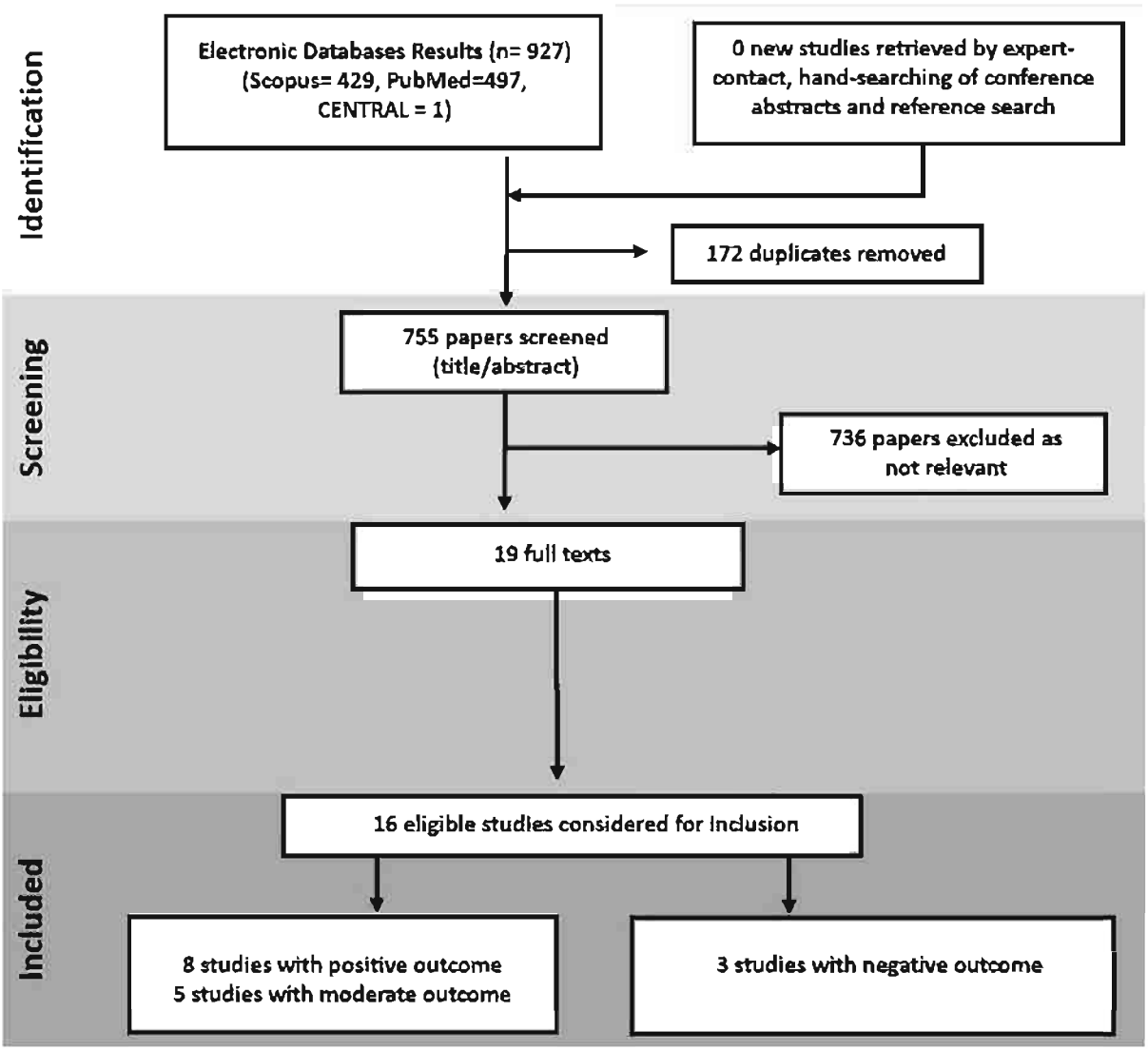

Figure 11. Flowchart for selection of articles based on PRISMA general principles for the use of melatonin in shift-work disorder.

The following Table summarises the methods, population groups, regimens as well as efficacy and safety outcomes of 16 clinical studies published from 1993 till 2018, involving about 550 adult (night) shift workers. Among them, 13 studies used IR melatonin tablets [redacted] or caplets [redacted] and 3 SR melatonin tablets [redacted] The SR melatonin studies were provided for supportive purposes only, in order to assist the evaluation of efficacy and safety of melatonin in this claimed indication. Of the 16 tabulated studies, 13 were randomised, placebo-controlled crossover trials [redacted] 1 had a crossover design [redacted] 1 was randomised triple placebo controlled trial [redacted] and 1 was a preliminary double-blind study [redacted] Among the IR studies, 8 trials administered melatonin in the morning after the night shift and before the daytime sleep period [redacted] **The doses of melatonin varied between 1 mg [redacted] to 10 mg [redacted] doses in all trials mostly lied between 3 and 6 mg.** All trials reported on the effect of orally administered melatonin on sleep length and quality after one or several consecutive night shifts. Six trials evaluated daytime sleep after the night shift, during a night shift period of several consecutive nights [redacted] Two trials evaluated both daytime sleep during the night shift and night-time sleep after the night shift period [redacted] Four trials evaluated night sleep after the night shift period [redacted] The majority of trials concluded in a positive efficacy outcome and favourable safety of melatonin administration in shift workers, 3 studies found no significant effect and 5 concluded on moderate effects, where melatonin improved sleep in some of the workers but did not increase night-time alertness.

Table 19. Clinical studies identified in the literature investigating the efficacy of oral melatonin administration for the management of SWD in adults. ***Keynote:*** *Red colour denotes lack of effect, yellow colour denotes moderate effects and green colour denotes favourable efficacy results.*

Reference	Design	Objective (s)	Efficacy endpoints	Duration of treatment	Study sample (subjects, condition)	Dosing regimen	Efficacy results
[redacted]	Preliminary double-blind study (United Kingdom)	To examine the effects of melatonin on sleep, mood and behaviour in police officers working spans of 7	Sleep, mood and midshaft performance measures	2 × 14 days	17 healthy volunteer police officers (15 men and 2 women, aged 21-48 years	**Melatonin 5 mg** in lactose gelatine capsule or placebo, taken prior to each of the 6 successive day sleeps taken between the	Compared to placebo and to no treatment (baseline), melatonin received at the desired bedtime improved problems related to sleep and increased alertness during working hours, especially during the early morning. In letter-target performance tests visual

Reference	Design	Objective (s)	Efficacy endpoints	Duration of treatment	Study sample (subjects, condition)	Dosing regimen	Efficacy results
[redacted]		successive night shifts.				night shifts at 06:42 ± 7.6 min (and prior to each of the following 4 normally timed night sleeps at 00:39 h ±12.7 min)	search speed and accuracy were either unchanged or slightly improved.
	Randomised triple placebo-controlled trial (Australia)	To compare the efficacy of nocturnal bright light and daytime administration of melatonin with a placebo group to improve sleep and performance measures during a 3-day transition to night shift.	Circadian phase, core temperature, sleep quality, cognitive performance.	3 days	36 male and female subjects aged 18-30 years of age (mean ± SD age: 23.6±3.9 years)	Either timed exposure to bright light between 24:00 and 04:00 on each of 3-night shifts (n=8), **melatonin capsules 2 mg at 08:00 then 1 mg at 11:00 and 14:00** (n=12) or placebo light/capsule (n=16).	All groups shifted significantly from baseline. Using the DLMO as a circadian marker, the bright-light group shifted the furthest, whereas there was no significant difference between the melatonin and placebo groups. Sleep quality (measured by wrist actigraphy) was most improved in the light-treatment group, although the melatonin group also showed significant improvements. Although melatonin was unable to increase the amount of the phase shift after transition to night shift, it is likely that the intermediate levels of improvement in sleep reflect the hypothermic effects of melatonin. By lowering core temperature across the sleep period, sleep may be enhanced. This improvement in sleep quality did not produce concomitant improvements in shift performance for melatonin group.
	Double-blinded, randomised, crossover study (US)	To determine whether melatonin is effective in helping emergency medical services personnel who work rotating night shifts reset their biological clocks and minimise circadian rhythm disruption.	Assessment of sleep quality, posttreatment mood and workload ratings.	Each participant completed a total of 4 spans of consecutive night shifts (2 melatonin, 2 placebo)	22 healthy adult volunteers who were working a span of consecutive night (23:00 to 07:00) shifts	Either a **melatonin 6-mg capsule (Vitamin Research Products Inc., Carson City, Nevada)** or placebo to be **taken before each of the consecutive day sleeps.**	Analysis of sleep diaries found no significant difference ($P>.05$) between the two treatments with respect to mean SL, duration and efficiency and subjectively rated sleep quality. No significant benefits were noted between the median VAS scores for daily post-treatment mood or workload ratings. Hence, no clinical benefits were noted in the personnel working rotating night shifts.
	Double-blind, placebo-controlled crossover trial (US)	To determine whether exogenous melatonin improves day sleep or night alertness in	Time at the start and end of a sleep period, sleep duration, time required to fall asleep, desired	2-5 days	18 emergency physicians (adults) who worked strings of 2 or 5 daily 8-h night shifts	Either **10 mg sublingual melatonin tablet (Source Naturals Products, Scotts Valley,**	As measured on the basis of SSS, melatonin improved alertness at the end of a night shift over placebo (MD, 0.5; 95% CI, 0.04-1.0). No difference was noted between melatonin

Reference	Design	Objective (s)	Efficacy endpoints	Duration of treatment	Study sample (subjects, condition)	Dosing regimen	Efficacy results
[redacted]		emergency physicians working night shifts.	sleep duration, number of premature awakenings, and number of sleep periods stopped early because the subject could not sleep, quality of sleep.		(23:00 to 07:00)	CA.) or placebo **each morning during one string of nights** and the other substance during another string of nights of equal duration.	and placebo in alertness at the beginning of a night shift (median, 0; 95% CI, –0.4 to 0.9) or at the midpoint of a night shift (median, 0; 95% CI, –0.4 to 0.5). When the melatonin and placebo periods were combined, median SSS scores increased as night shifts progressed from 2 just before a shift to 2.25 at midpoint, to 4.75 just after a night shift.
	Randomised, placebo-controlled, double-blind, crossover trial (US)	To determine whether there are measurable beneficial effects from exogenous melatonin in emergency physicians after intermittent night-shift duty.	SL (min), hours sleep per night, night awakening (mean number awakenings), early awakening	3 nights	15 physicians (adults) from the emergency department of an urban tertiary care hospital	**Melatonin 5 mg (as 2 melatonin 2.5-mg tablets; Nature's Vision, Portage, MI)** or placebo **for 3 consecutive nights after night-shift duty** with crossover to the opposite agent after a subsequent block of night shifts.	There was no difference between melatonin and placebo in the global assessment of recovery (60.4±16.9 and 58.9±14.5, respectively; P=0.29). There were no differences in sleep quality, duration or tiredness scores, sleep latency, hours of sleep obtained per night and night or early awakening at any measurement point. Profile of mood states and neuropsychologic test performances were similar. No beneficial effect of melatonin was found on sleep quality, tiredness, or cognitive function in emergency physicians after night-shift duty. The results suggest that exogenous melatonin is of limited value in recovery from night shift work in emergency physician.
	Prospective, randomised, double-blind crossover design (US)	To determine whether melatonin taken prior to attempted daytime sleep sessions will improve daytime sleep quality, nighttime sleepiness, and mood state in emergency medicine residents, changing from daytime to nighttime work schedules.	Assessment of daytime sleep quality, nighttime sleepiness, and mood state in emergency medicine residents, changing from daytime to nighttime work schedules.	3 days	19 emergency medicine residents (adults)	Either **melatonin 1 mg caplet (Par Pharmaceuticals, Spring Valley, NY)** or placebo, **30-60 min prior to their daytime sleep session**, for 3 consecutive days after each night shift.	Among the 19 volunteers, there was no difference in sleep efficiency (91.16% vs 90.98%, not significant), sleep duration (379.6 vs 342.7 min, not significant) or SL (7.59 vs 6.80 min, not significant), between melatonin and placebo, respectively. In addition, neither the POMS total mood disturbance (5.769 baseline vs 12.212 melatonin vs 5.585 placebo, not significant) nor the SSS (1.8846 baseline vs 2.2571 melatonin vs 2.1282 placebo, not significant) demonstrated a statistical difference in nighttime mood and sleepiness between melatonin and placebo.

Reference	Design	Objective (s)	Efficacy endpoints	Duration of treatment	Study sample (subjects, condition)	Dosing regimen	Efficacy results
	Placebo-controlled, double-blind, crossover design (US)	To isolate the sleep-promoting effects of melatonin, and to determine whether melatonin could improve daytime sleep and thus nighttime alertness and performance during the night shift.	Daytime sleep, recovery sleep, salivary levels of melatonin, subjective reports of sleepiness, sleepiness during the night shifts, performance and mood during night shifts.s	Two 6-day laboratory sessions, including 1 adaptation night, 2 baseline nights, 2 consecutive 8-h night shifts followed by in 8-h daytime sleep episodes and 1 recovery night	21 (mean age: 27.0±5.0 years) subjects working night shifts	Subjects took **1.8 mg SR melatonin tablet** (donated by Ecological Formulas, Concord CA) **0.5 h before the 2 daytime sleep episodes** during 1 session, and placebo before the daytime sleep episodes during the other session.	Melatonin prevented the decrease in sleep time during daytime sleep relative to baseline, but only on the 1st day of melatonin dosing. Melatonin increased sleep time more in subjects who had difficulty in sleeping during the day. Melatonin had no effect on alertness on the MSLT or performance and mood during the night shift.
	Randomised double-blind design (US)	To test whether melatonin can facilitate phase shifts in a simulated night work protocol.	Circadian rhythm phase shifts, body temperature, sleepiness and mood ratings.		32 adult subjects who slept in the afternoons/ evenings before night work (a 7-h advance of the sleep schedule)	Either **melatonin 0.5 mg (n=9) or 3.0 mg** capsules (donated by Ecological Formulas, Concord CA) (n=11) or placebo (n=12) **before the first 4 of 8 afternoon/ evening sleep episodes** at a time when melatonin has been shown to phase advance the circadian clock.	Melatonin produced larger phase advances than placebo in the circadian rhythms of melatonin and temperature. Average phase advances (±SD) of the dim light melatonin onset were 1.7±1.2 h (placebo), 3.0±1.1 h (0.5 mg) and 3.9±0.5 h (3.0 mg). A measure of circadian adaptation, shifting the temperature minimum enough to occur within afternoon/evening sleep, showed that only subjects given melatonin achieved this goal (73% with 3.0 mg, 56% with 0.5 mg and 0% with placebo).
	Crossover design (Republic of Korea)	Whether melatonin improves adaptation of workers to nightshift and if its beneficial effect is enhanced by attenuation of morning sunlight exposure.	Daytime sleep, nocturnal alertness, performance, mood states.	for 2 days of different 4-day nightshifts	12 nightshift nurses (adults)	Placebo, **melatonin 6 mg pill** and melatonin with sunglasses for 2 days of different 4-day nightshifts. Placebo and melatonin were taken before daytime sleep and allowed exposure to morning sunlight.	The sleep period and TSTs were significantly increased by melatonin treatments. Nocturnal alertness was only marginally improved. There were no differences between melatonin groups. Performance tests revealed no difference between placebo and melatonin treatments. Melatonin exerted modest benefit in improving the adaptation of workers to nights hift and its effect was not enhanced by attenuation of morning sunlight exposure.
	Double-blind crossover trial (US)	To test the relative contribution and the combined	Circadian phase assessments.		67 young participants (median age: 22 years) participated	Sunglasses, bright light, **melatonin 1.8 mg SR tablet** (donated by	With bright light during the night shift, almost all of the earlier participants achieved complete re-entrainment and the phase delay shift

Reference	Design	Objective (s)	Efficacy endpoints	Duration of treatment	Study sample (subjects, condition)	Dosing regimen	Efficacy results
[redacted]		effectiveness of various interventions, i.e., bright light, sunglasses and melatonin to phase-delay circadian rhythms and realign them with sleep in the morning after night shift.			in 5 consecutive simulated night shifts (23:00 to 07:00) and then slept at home (08:30 to 15:30) in darkened bedrooms	Ecological Formulas, Concord, CA) or placebo right before bedtime at 08:30.	was so large that darker sunglasses and melatonin could not increase its magnitude With only room light during the night shift, darker sunglasses helped earlier participants phase-delay more than normal sunglasses, but melatonin did not increase the phase delay.
	Double-blind, randomised, placebo-controlled crossover study (US)	To test whether melatonin reduces the deleterious effects of night-shift work on sleep, mood and attention in paediatric residents during night float rotation.	Sleep, attentions and mood measures.	2 weeks	16 men and 29 women (healthy second-year paediatric residents working 2 night float rotations), aged 28.6±1.9 years, participated. Of these 45 residents, 28 participated in the study during the 2 night float rotations, completing the 2 treatment arms of the crossover design.	Either **melatonin 3 mg gelatine capsules** (containing synthesised melatonin by Regis Chemical Co. Morton Grove, Ill) mixed in lactose) or a placebo **before bedtime in the morning after night shift**	28 residents completed both treatments: 17 completed 1 treatment (10 placebo, 7 melatonin). There was not a statistically significant difference in measures of sleep, mood, and 5 of 6 measures of attention during melatonin and placebo treatment. One measure of attention, the number of omission errors, was significantly lower on melatonin (3.0±9.6) than on placebo (4.5±17.5) ($z = -2.12$, $P=0.03$). A beneficial effect of melatonin in attention may occur independently of improved sleep or decreased fatigue. However, melatonin did not improve sleep duration, vigour or fatigue. The variability in responses and the inconsistency of results among other studies may have been due to pharmacogenetic characteristics, individual tolerance to shift work and a relationship of response to melatonin with individual tolerance to shift work.
	Double-blind crossover trial	To determine whether melatonin had a soporific effect.	Sleep log measurements of TST and actigraphic measurements of SL, TST and three movement indices.		36 adult participants who worked 5 consecutive simulated night shifts, from 23:00 to 07:00 h	**Melatonin 1.8 mg SR tablets** (by Ecological Formulas, Concord, California) (n=18) or placebo (n=18), taken at 10:00 h.s	Although melatonin was associated with small improvements in sleep quality and quantity, the differences were not statistically significant by AVOVA. However, binomial analysis indicated that melatonin participants were more likely to sleep better than their placebo counterparts on some days with some measures.
	Randomised, controlled crossover design	To evaluate the effects of bright light and melatonin on adaptation	Subjective and objective measures of sleepiness (KSS and a	8 days	17 subjects working a schedule of 2 weeks on a 12-h shift,	Placebo, **melatonin 3 mg caspule, 1 h before bedtime**, or	Subjective measures showed that melatonin modestly reduced sleepiness at work during the day shift and increased

Reference	Design	Objective (s)	Efficacy endpoints	Duration of treatment	Study sample (subjects, condition)	Dosing regimen	Efficacy results
	(Norway and Sweden)	to night work on an oil rig in the North Sea.	simple serial reaction-time test) and sleep (diary and actigraphy).		with the 1st week on night shift and the 2nd week on day shift (i.e., swing shift schedule)	bright light (30-min exposure) during the first 4 days on the night shift and during the first 4 days on the day shift.	sleep by 15-20 min per day. Bright light gave values in between those of melatonin and the placebo, but with few significant results. According to objective measures, bright light improved sleep to a minor degree during night shift.
	Double-blind, randomised, placebo-controlled crossover study (Iran)	To evaluate the effect of oral melatonin taken before nighttime sleep on subjective sleep onset latency, number of awakenings and duration of sleep.	Subjective sleep onset latency, number of awakenings and duration of sleep.	1 night	118 shift-worker nurses, aged 24-46 years	Oral intake of **5 mg melatonin tablet taken 30 min before nighttime sleep** or placebo, on the first night after night work.	Sleep onset latency was significantly reduced while subjects were receiving melatonin as compared with both placebo and baseline. There was no evidence that melatonin altered TST (as compared with baseline TST).
	Randomised, double-blind, placebo-controlled crossover study (Iran)	To evaluate the efficacy of 3 mg melatonin taken 30 min before nighttime sleep on shift workers with difficulty falling asleep.	sleep efficiency, sleep onset latency, TST, wakenings after sleep onset.	Duration of study was 20 days (3 nights each period with a washout of 2 weeks)	50 adult shift workers with difficulty falling asleep (mean age: 32.9±8 years)	**Melatonin 3 mg tablet** or placebo, **taken 30 min before nighttime sleep.**	Among 295 workers, 103 had difficulty falling asleep. Finally, from 50 randomly selected workers with difficulty falling asleep, 39 workers completed the study. Melatonin treatment significantly increased sleep efficiency and decreased sleep onset latency vs baseline and placebo. Sleep efficiency was increased from 82.1% at baseline to 85.5% after melatonin therapy. Also, sleep onset latency was decreased from 0.27 h at baseline to 0.20 h after melatonin. Effects of melatonin on TST and wakening after sleep onset were not significant.
	Randomised, double-blind, replicated crossover trial (Iran)	To compare the effectiveness of melatonin vs placebo on sleep efficiency in emergency medicine residents.	Primary: comparison of KSS and POMS scores between the 2 arms. Secondary: comparison of other sleep quality variables between the 2 arms.	2 nights	24 emergency medicine residents (adults) working 9-h shifts on 6 consecutive days, 2 mornings, 2 evenings and 2 nights and then 2 days off	**At the end of shifts' cycle, 3 mg melatonin tablet** or placebo (12/arm) for 2 consecutive nights after the 2nd night shift with crossover to the other arm after a 6-day off drug	In the melatonin group, daytime sleepiness (calculated by KSS) had a significant reduction after taking the 2nd dose of drug (P=0.003), but the same result was not observed when comparing the 2 groups. Mood status (calculated by Profile of Mood States) showed no remarkable difference between the 2 groups.

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; DLMO, dim-light melatonin onset; KSS, Karolinska Sleepiness Scale; MD, median difference; MSLT, multiple sleep latency test; POMS, Profile of Mood States; SD, standard deviation; SL, sleep latency; SR, sustained release; SSS, Stanford Sleepiness Scale; TST, total sleep time; US, United States; VAS, visual analogue scale.

In an open study [redacted], in which a total of 1,533 nurses participated in a survey on shift work, sleep and health responded to questionnaires at baseline and about 2 years later at follow-up, the results showed a significant reduction in the prevalence of SWD from baseline to follow-up, from 35.7% to 28.6%. Significant risks of having SWD at followed-up and the following variables measured at baseline; number of nights worked the last year (odds ratio [OR]=1.01, 95% CI= 1.01-1.02), having SWD (OR=5.19, 95% CI= 3.74-7.20), composite score on the Epworth Sleepiness Scale (OR=1.08, 95% CI= 1.04-1.13), use of melatonin (OR=4.20, 95% CI= 1.33-13.33), use of bright light therapy (OR=3.10, 95% CI= 1.14-8.39), and symptoms of depression measured by the Hospital Anxiety and Depression Scale (OR=1.07, 95% CI= 1.00-1.14). Leaving night work between baseline and follow-up was associated with a significant reduced risk of SWD at follow-up (OR=0.12, 95% CI= 0.07-0.22).

An early meta-analysis by [redacted] suggested a combined estimate produced by the studies that favored melatonin in the treatment of secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and SWD, however, the effect was not significant. Nevertheless, the analysis provided evidence that melatonin is safe with short-term use in such conditions [redacted] of the studies conducted by [redacted], the majority of studies of permanent night-shift workers have found melatonin to be of benefit in facilitating circadian adaptation to night-shift work.

[redacted] attempting a practical approach to circadian rhythm disorders, concluded that bright light treatment and exogenous melatonin administration are considered to be the treatments of choice for these circadian rhythm sleep disorders, including SWD, although melatonin treatment is not dose-related. A subsequent review *by* [redacted] suggested that melatonin (1.8-6 mg), given prior to day sleep, has been shown to improve total sleep duration in both simulated night shifts and studies of night workers, being a rational treatment option for shift work requiring an early rise time, due to the known efficacy of exogenous evening melatonin in advancing circadian rhythms. A corresponding review article published in the same year by [redacted] stated that studies on the effectiveness of melatonin for the treatment of SWD have been mixed and conclusions may be limited by the use of different doses and formulations, however melatonin or other hypnotic administered before daytime sleep is suggested as a possible treatment for SWD. [redacted] also presented a non-systematic review of all potential uses of melatonin and concluded that for shift work related sleep problems results were inconclusive due to the variability of the sourced data.

A Cochrane systematic review of 15 randomised placebo-controlled trials with 718 participants included 9 trials that evaluated the effect of melatonin and 2 for the effect of hypnotics for improving sleep problems. One trial assessed the effect of modafinil, 2 of armodafinil and 1 examined caffeine plus naps to decrease sleepiness or to increase alertness. Melatonin (1-10 mg) taken after the night shift may increase sleep length during daytime sleep (mean difference [MD]=24 min, 95% CI, 9.8-38.9; 7 trials, 263 participants, low quality evidence) and night-time sleep (MD=17 min, 95% CI, 3.71-30.22; 3 trials, 234 participants, low quality evidence) compared to placebo. The investigators did not find a dose-response effect. Most trials were judged to have a low risk of bias even though the randomisation method and allocation

concealment were often not described [redacted] In addition, according to the conclusions of a very recent systematic review of 10 clinical studies [redacted] administration of exogenous melatonin, at doses ranging from 1 to 10 mg, was overall considered effective in shift worker health personnel suffering from sleep disorders and given its low AEs and tolerability, it received a favorable opinion by the study authors.

In order to more clearly define the actual outcomes of literature studies, the Applicant has performed a thorough re-analysis of clinical data based on the Cochrane systematic review of [redacted] The effects of melatonin administration on various subjective and objective endpoints, regarding the physiological effects of SWD, were evaluated so as to conclude if there is a proper dosing scheme of melatonin supplementation for this indication. Sleep time (next day and next night), sleep onset latency (next day and next night), sleep quality (assessed by VAS), alertness during the night shift work (assessed by VAS) and sleepiness during the night shift work (assessed by KSS) were assessed (Table 20).

Table 20. Overall statistical data on the effect of melatonin on SWD.

Outcome or subgroup title	Number of studies	Statistical method	Effect size
Total sleep time, next day	7	Mean Difference (IV, Fixed, 95 % CI)	24.34 [9.82, 38.86]
Diary-based sleep time	6		23.49 [8.49, 38.49]
Actigraphy based sleep time	1		37.0 [-20.87, 94.87]
Total sleep time, next night	3		16.97 [3.71, 30.22]
Diary-based sleep time	2		19.05 [4.47, 33.63]
Actigraphy-based sleep time	1		7.0 [-24.88, 38.88]
Sleep onset latency, next day	5	Mean Difference (IV, Random, 95 % CI)	0.15 [-2.18, 2.48]
Diary-based sleep onset latency	4		0.80 [-1.15, 2.75]
Actigraphy-based sleep onset latency	1		-9.0 [-18.60, 0.60]
Sleep onset latency, next night	3		Totals not selected
Diary-based sleep onset latency, next night	2		0.0 [0.0, 0.0]
Actigraphy-based sleep onset latency, next night	1		0.0 [0.0, 0.0]
Sleep quality (VAS)	4	Std. Mean Difference (IV, Fixed, 95 % CI)	0.08 [-0.15, 0.31]
Alertness during the night shift work (VAS)	1		Totals not selected
Sleepiness during the night shift work (KSS)	1		Totals not selected
Sleepiness during the day shift work (KSS)	1		Totals not selected
Abbreviations: CI, confidence interval; KSS, Karolinska Sleepiness Scale; VAS, Visaul Analogue Scale.			

Taking everything above into consideration, **administration of 1-10 mg (more frequent dose was 3-6 mg) melatonin** after the night shift may increase sleep length during daytime sleep (MD=24 min, 95% CI: 9.8-38.9; 7 trials, 263 participants) and night-time sleep (MD=17 min, 95% CI: 3.71-30.22; 3 trials, 234 participants) compared to placebo, but will probably have no effect on sleep latency in next day or night. Additionally, there is substantial evidence that melatonin is safe with short term use and the AEs reported from these studies did not differ statistically significant from that of placebo (please refer to Table 21 below).

Therefore, **the proposed indication of management of SWD and the dosing scheme of 3-6 mg melatonin supplementation one hour before bedtime may be generally supported by the current scientific literature for the oral solution of 1 mg/ml melatonin** due to its beneficial effect in sleep length during daytime and night-time, lack of AEs in other sleep

parameters and excellent safety profile. In all, literature evidence supports the notion that melatonin can be considered as an effective agent in helping shift workers manage sleep and alertness better, provided that the right dose at the right time is employed. Of note, the management of shift-work sleep disorder has been already included as an indication for other commercially available melatonin tablet formulations marketed since early 00's in some EU member states [redacted]. Although some of the published trials have also utilised solid formulations, it has to be taken into consideration that the bioavailability of the liquid forms is comparable to those of the IR solid forms (please refer to the Pharmacokinetics Section of the current Clinical Overview), with the PK parameters being within the range and approaching the mean of those obtained with the solid dosage forms; therefore, bridging is successfully met.

2.5.4.4 DOSING SCHEDULE AND ADMINISTRATION

Altogether, taking into account both PK and clinical data, the proposed posology recommendations are as follows, also according to other approved melatonin products for the proposed indications and patient population groups.

Posology

For the short-term treatment of jet lag in adults

The standard dose is 3 mg (3 ml) daily for a maximum of 5 days. The dose may be increased to 6 mg (6 ml) if the standard dose does not adequately alleviate symptoms. The dose that adequately alleviates symptoms should be taken for the shortest period. The first dose should be taken on arrival at destination at the habitual bedtime. Due to the potential for incorrectly timed intake of melatonin to have no effect or an AE, on re-synchronisation following jet lag, melatonin 1 mg/ml oral solution should not be taken before 20:00 h or after 04:00 h at destination. Melatonin 1 mg/ml oral solution may be taken for a maximum of 16 treatment periods per year.

Sleep onset insomnia in children and adolescents aged 6-17 years with ADHD

Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine.

Recommended starting dose is 1-2 mg (1.0-2.0 ml) 30-60 min before bedtime. The dose can be increased by 1 mg (1.0 ml) every week until effect up to a maximum 6 mg (6 ml) per day, independent of age. The lowest effective dose that controls symptoms should be given.

There is limited data available for long-term treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider discontinuing the treatment if no clinically relevant treatment effect is seen. The patient should be monitored at regular intervals (at least every 6 months) to check that melatonin 1 mg/ml oral solution is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly at least once per year.

If insomnia has occurred during treatment with ADHD medication, dose adjustment or change of the treatment should be considered.

Management of SWD in adults

The recommended starting dose is 3 mg (3 ml) before bedtime. The dose can be increased until effect to a maximum 6 mg (6 ml) per day.

Elderly

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

Renal impairment

There is only limited experience regarding the use of Melatonin 1 mg/ml oral solution in patients with renal impairment. Caution should be exercised if melatonin is used by patients with renal impairment. Melatonin 1 mg/ml oral solution is not recommended for patients with severe renal impairment.

Hepatic impairment

There is no experience regarding the use of Melatonin 1 mg/ml oral solution in patients with hepatic impairment. Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis. Melatonin 1 mg/ml oral solution is not recommended in patients with moderate or severe hepatic impairment.

Paediatric population (under 6 years of age)

The safety and efficacy of Melatonin 1 mg/ml oral solution in children aged 0-6 years have not been established.

Method of administration

Melatonin 1 mg/ml oral solution is for oral use only.

Once titrated to an effective dose of Melatonin oral solution, patients may remain on their treatment and care should be exercised when changing between different formulations. Food can enhance the increase in plasma melatonin concentration.

Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours. It is recommended that food is not consumed 2 h before and 2 h after intake of Melatonin 1 mg/ml oral solution. As alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g., headache, morning fatigue, concentration), it is recommended that alcohol is not consumed when taking Melatonin 1 mg/ml oral solution.

2.5.5 OVERVIEW OF SAFETY

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

2.5.5.1 TOXICITY

There is an amount of published information regarding the potential AEs of melatonin. Melatonin is considered to be safe, as being an endogenous substance that is well-tolerated even when administered at high doses (100 mg crystalline melatonin). The most commonly reported adverse reactions of short-term melatonin use were nausea (incidence: ~1.5%), headache (incidence: ~7.8%), dizziness (incidence: 4.0%) and drowsiness (incidence: 20.3%); however, these effects were not significant compared to placebo. Melatonin treatment appeared to be well-tolerated in patients [redacted] This result did not change by dose, the presence or absence of a sleep disorder, type of sleep disorder, duration of treatment, gender, age, formulation of melatonin, use of concurrent medication, study design, quality score and allocation concealment score [redacted]. Overall, AEs were generally minor, short-lived and easily managed, with the most commonly reported AEs relating to fatigue, mood or psychomotor and neurocognitive performance. Melatonin doses below 8 mg have occasionally induced heavy head, headache and transient depression [redacted]

Although it has been referred that melatonin may aggravate depression in patients with psychiatric illness or induce it in those susceptible to it [redacted] in a systematic review conducted by [redacted], 10 studies reporting on psychological AEs, such as depression, anxiety or mood changes, found no statistically significant difference between melatonin and placebo [redacted] Therefore, the potential aggravation of depression due to melatonin is not considered to be clinically relevant in short-term administration of therapeutic doses or as supplement. In animal models, melatonin treatment significantly abolished the effects of lipopolysaccharide and reduced nuclear factor-kappaB (NF-κB) in the cortex and the hippocampus, both effects resulting in an improvement of depressive-like behaviours [redacted] These results point towards the possibility of an "antidepressant effect" of melatonin via the interplay with the immune system. Furthermore, cortisol functioning and its circadian fluctuation is essential for the adequate melatonin surge. Blunted cortisol rhythms (i.e., lower morning cortisol peak and higher daytime values) have been demonstrated in association with depressive symptoms in humans [redacted] A significant increase in fatigue with melatonin administration, alongside decrease in vigour/energy, has been reported in studies in which melatonin was administered during daylight hours at higher doses (>50 mg) [redacted]

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

Suppression of endogenous melatonin secretion

Exogenous melatonin did not affect the production of endogenous melatonin in terms of secretion rate, amplitude and duration. [redacted] measured the endogenous melatonin profiles after a physiological dose of melatonin (0.5 mg) or placebo at bedtime to 21 night-shift workers for 7 days. The amplitude of endogenous melatonin secretion was unchanged by treatment. Also, a melatonin treatment trial using a 50-mg daily bedtime dose for 37 days to a blind subject resulted in no change in the endogenous melatonin profile.

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

Hepatotoxicity

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

The use melatonin is not recommended for use in patients suffering from moderate or severe hepatic impairment.

Cardiovascular system

AEs on BP and heart rate in populations with cardiovascular conditions and concurrent antihypertensive medications have been reported with melatonin use. However, it is unclear whether these events are attributable to melatonin itself or to melatonin-drug interactions. The

lack of information concerns also several other conditions, including autoimmune disorders, interactions with commonly used medicines, etc [redacted]

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

Glucose metabolism

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

CNS adverse reactions

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

A later comprehensive, critical systematic review of clinical evidence examined controlled studies of oral melatonin supplementation in humans when they presented any statistical

analysis of AEs. Of the 50 articles identified, 26 found no statistically significant AEs while 24 articles reported on at least one statistically significant AE. AEs were generally minor, short-lived and easily managed, with the most commonly reported AEs relating to fatigue, mood or psychomotor and neurocognitive performance. A few studies noted AEs relating to endocrine (e.g., reproductive parameters, glucose metabolism) and cardiovascular (e.g., blood pressure, heart rate) function, which appear to be influenced by dosage, dose timing and potential interactions with antihypertensive drugs. Oral melatonin use in humans has a generally favourable safety profile. It has been suggested that most AEs can likely be easily avoided/managed by dosing according to natural circadian rhythms [redacted]

Epilepsy

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

A study found no suggestion that long-term intake of melatonin activated an epileptic event in 19 paediatric patients with a seizure disorder. A study in which 51 children and young adults with intellectual disability were treated with melatonin or placebo for 4 weeks observed no changes in seizure frequency [redacted]. A 3.7-year follow-up study of 101 children with ADHD who had previously been given 3-6 mg melatonin for 4 weeks found none to have developed epilepsy, a finding considered consistent with literature data indicating no clear pro-convulsive action of melatonin [redacted]. A review of melatonin for sleep disorders associated with intellectual disability noted that while a few studies have reported worsening or development of seizures after initiation of melatonin, a number of others have not found melatonin to have such effects and that it may actually have beneficial effects on seizures [redacted]. A recent review of the potential for melatonin to affect epileptic seizures identified 3 RCTs of which 2 showed no overall worsening or improvement in seizures and the third a statistically significant reduction in seizures. The open studies identified conflicting results, therefore, the available data were considered limited [redacted]

Acute toxicity (short-term use)

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

Acute administration of melatonin appears to have little consistent effect on hormone levels in adult humans. Several early studies indicated effects of melatonin on GH secretion in men, whereas a comprehensive study has indicated that the only acute effect of melatonin was an elevation in prolactin levels, as determined in 24 young healthy males after oral administration of 240 mg melatonin. Melatonin received in sufficiently high doses may also enhance GH levels, whereas various other hormones are not influenced [redacted]

Chronic toxicity

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

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

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

From the above presented safety data, it can be concluded overall that melatonin doses of 0.5-6.0 mg can be used safely in adults and children (6-18 years) for the proposed indications, based on the identified literature data, reports, safety reviews and the clinical experience with the already marketed products. A more detailed discussion on the safety aspects based on the data from respective clinical trials for the adults' and paediatric patients according to claimed indications in this submission, is presented in the following subsections (2.5.5.1.1 Safety in adults and 2.5.5.1.2 Safety in paediatric patients).

2.5.5.1.1 Safety in adults

Below, the AEs encountered in clinical studies investigating the usefulness of melatonin for jet lag and SWD and its general toxicological and safety profile in order to cover the case of overdose, contraindications and interactions are thoroughly presented. Both indications require only low doses of melatonin.

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

In the studies reviewed in the Section *'2.5.4.1 Overview of Efficacy'*, the most commonly reported AE was daytime sleepiness that can be limited by lowering the dose administered, without impairing the efficacy. The following Table summarises the AEs observed in RCTs involving melatonin administration for treatment of jet lag and SWD in adults and for sleep disorders in children with ADHD.

Table 21. Tabulated observations of AEs noticed in RCTs investigating the efficacy and safety of melatonin in the treatment of jet lag as well as in randomised trials in shift workers given melatonin.

Reference	Melatonin dose	Number of subjects	Safety results
Jet lag in adults			
[redacted]	5 mg	586 (474 melatonin, 112 placebo)	AEs reported more than once are (melatonin %-placebo %): sleepiness (8.3%- 1.8%), headache (1.7%-2.7%), nausea (0.8%-0.9%), "fuzziness/giddiness" (0.6%-0%) and light-headedness (0.5%-0%).
	0.5, 2.0 or 5.0 mg	234 (174 melatonin, 60 placebo)	The incidence of AEs had no difference between the 4 groups (placebo, 0.5 mg, 2.0 mg, 5.0 mg of melatonin). Most of the reported symptoms were the most common ones for jet lag, such as daytime sleepiness, headache, dizziness or loss of appetite; these decreased with each treatment day and with equivalent incidence in melatonin- and placebo-treated groups.
	5 mg	137 (5 melatonin, 29 melatonin+ zolpidem, 39 placebo)	Combination melatonin/zolpidem were less well-tolerated than melatonin alone; AE reports included nausea, vomiting, amnesia and somnambulia to the point of incapacitation. Confusion, morning sleepiness and nausea were highest in the combination group.
	5 mg	26 (13 melatonin, 13 placebo)	A total of 6 subjects reported an increased number of headaches, 4 subjects reported dizziness and 6 subjects described a disorientating 'rocking' feeling. There was no significant difference between the melatonin and placebo groups for headaches and dizziness, but 5 of the 6 subjects who reported a 'rocking' sensation were in the melatonin group.
	5 mg	61 (crossover)	Infrequent AEs included drowsiness, headache, and nausea.
	8 mg	37 (22 melatonin and 15 placebo)	Two cases of AEs were related to the hypnotic activity of melatonin. A single case of tachycardia and 2 cases of 'heavy head' were considered to be of minor consequence.

[redacted]	0.5 or 5.0 mg	257 (197 melatonin, 60 placebo)	There was no significant difference in the number of subjects reporting AEs within the active treatment groups or within the placebo group. In one subject receiving 0.5 mg melatonin, difficulty swallowing, and breathing was reported almost 20 min after ingestion, symptoms that subsided after 45 min. Similar symptoms, although somewhat milder, did reccur also in other volunteers.
	5 mg	20 (crossover)	No AEs with either placebo or melatonin. Two subjects taking melatonin reported a mild sedative effect lasting about 0.5 h and 1 other reported feeling more relaxed. Among subjects taking placebo, 1 reported increased tiredness, 1 a greater feeling of relaxation and 1 a greater depth of sleep.
	5 mg	44 (29 melatonin, 15 placebo)	5 of the 18 volunteers receiving pre-flight melatonin reported minor AEs. Two had sleeping difficulties after beginning the capsules, 1 felt drowsy for a brief time after taking melatonin. 1 complained of occasional headaches and another felt depressed for 1 day after returning home. None of the subjects in the group receiving melatonin only after arrival or placebo reported AEs from taking the capsules 10 days.
	SWD in adults		
	5 mg	17	The mean ratings for "demands on your time" (time pressure), "mental effort or concentration" (mental load) and "stress or emotional involvement" (stress/emotional) were averaged over the 7 successive nights under each condition. The most interesting finding was the increased rating of mental workload under melatonin, with 5 of 6 subjects showing an increase relative to baseline and 4 of 6 showing an increase relative to placebo. This may imply either that melatonin tended to reduce the subjects' ability to cope with their mental work, or that there was an increase in mental workload on this leg of the study.
	2 mg	36 (12 melatonin, 8 bight light, 16 placebo)	*Post hoc* comparisons between each of the treatment groups and the placebo group indicated that the light group responded significantly faster than the placebo and melatonin groups across all 3-night shifts. There were no differences in mean correct response times between the melatonin and placebo groups on any of the shifts. Cognitive psychomotor performance was most improved in the light-treatment and the melatonin group again showed little difference from controls.
	6 mg	22	AEs were rare; 1 patient taking melatonin reported a prolonged sedative effect.
	10 mg	18 (crossover design)	Two subjects noted side effects. One experienced headache while taking melatonin, as well as nausea, abdominal cramping and irritability while taking placebo. The other subject reported excessive sedation at home while taking placebo.
	5 mg	15 (crossover design)	Melatonin was well tolerated by all subjects and no significant AEs were reported. Subjective tolerance scores were similar between the 2 groups. Two subjects reported headaches, both in the placebo phase of the trial.
	1 mg	19 (crossover design)	One subject described vivid dreams for one night while taking melatonin. Additionally, he reported difficulty changing back to a normal nighttime sleep session for 1 day after the experiment. The same subject also reported an increase in psychosocial stressors at the time of experiment due to unrelated personal circumstances. Otherwise, no AEs were reported.
	1.8 mg	21 (crossover design)	There were no hangover effects from melatonin administration.
	6 mg	12 (crossover design)	Performance tests revealed no difference between placebo and melatonin treatments.
	3 mg	28 (crossover design)	There was not a statistically significant difference between placebo and melatonin in the number of days with headache, abdominal pain, nausea, vomiting, diarrhoea or dizziness. Excessive sleepiness was present 10 days in 6 residents on placebo and only 1 day in 1 resident on melatonin treatment (not statistically significant difference (z= -21.69, P=0.09). One resident reported 5 days with nightmares during daytime sleep while taking melatonin.
	3 mg	17 (crossover design)	The participants reported very little discomfort or side effects from the different treatments. Of a total of 51 registrations (17 participants, 3 conditions), discomfort and side effects were recorded only 4 times. One participant reported headache after placebo; one reported headache plus eye discomfort, one experienced intensified dreaming following melatonin and one reported headache after exposure to bright light.
	5 mg	83 (crossover design)	No AEs of melatonin were noted during the treatment period.
	3 mg	24 (crossover design)	The most common side effects observed in the placebo group were lightheadedness (20.8%), abdominal cramps (12.5%) and some other minor AEs (20.8%). Conversely 11 residents (45.8%) reported no side effects. The most common side effects observed in the melatonin group were headache (16.7%), lightheadedness (12.5%), nausea (8.3%), vomiting (8.3%), abdominal cramps (8.3%) and some other minor AEs (4.2%). Conversely 10 residents (41.7%) reported no side effects. Finally, Chi-Square analysis showed no significant difference in AEs between the 2 groups (P=0.069).

Abbreviations: AE, adverse event.

2.5.5.1.2 Safety in paediatric patients

Safety information summarised below indicates that short-term use (days, i.e., weeks) and intermediate-term (e.g., months) use of exogenous melatonin is generally safe in paediatric patients with ADHD who suffer from sleep disorders. Safety data from studies of melatonin for insomnia in children with neurodevelopmental disorders, including ADHD, indicate that the drug is well-tolerated among this age population group and that the reported AEs (headache, nausea, decrease of appetite, dizziness and decrease of mood) and their frequency are often comparable to those in subjects receiving placebo. No serious AEs were observed following ingestion of typical therapeutic doses of melatonin in the individual studies (Table 22), which is also supported by reviews addressing specific and general aspects of melatonin safety (referring to adult and paediatric populations). As per the conclusion of a recent review by [redacted], severe AEs, such as migraine and mild generalised epilepsy, were reported in two cases. Data for long-term use of melatonin are available for children (aged 6 years and over) and adolescents, though specifically designed long-term safety studies are lacking in adults.

There is substantial evidence that melatonin is safe with short term use and the AEs reported from these studies did not differ statistically significant from that of placebo (please refer to Table 22 below).

Table 22. Tabulated observations of AEs noticed in randomised trials investigated the efficacy and safety of melatonin in children with ADHD suffering from sleep disorders.

Reference	Melatonin dose	Number of subjects	Safety results
[redacted]	5 mg	40 (20 melatonin, 20 placebo)	Mild headache occurred in 2 children during the first 2 days of melatonin treatment. Twelve children used melatonin 5 mg, the other 1.0-2.5 mg. One child developed mild generalised epilepsy 4 months after the start of the trial. The results show that melatonin, 5 mg at 18:00 was relatively safe to take in the short-term. Sustained attention was not affected.
	3 mg	27	Once a restless sleep was mentioned as a minor side-effect.
	5 mg	62 (27 melatonin, 35 placebo)	In the melatonin group, 7 parents reported cold feeling, decrease of appetite, dizziness and decrease of mood after first intake of the trial drug. In the placebo group, 3 parents reported headache, nausea, dizziness and increase of appetite. These possible AEs recovered within 3 days after the start of the trial medication.
	3-5 mg	33	No AEs were reported.
	5 mg	19 (crossover design)	AEs were generally mild and not different from those recorded with placebo treatment.
	3 or 6 mg	105 (53 melatonin, 52 placebo)	The number of AEs did not differ significantly between melatonin and placebo nor between the 3- (8/44) and 6-mg (2/9) treated groups (P=1.00). Five patients had 1 AE, 4 patients had 2 AEs and 1 had 3 AEs. There were no discontinuations or withdrawals due to AEs and none of the AEs required treatment.
	3-6 mg	94	3.7-year follow-up data (related to the study by *Van der Heijden et al., 2007*): No SAEs or treatment-related co-morbidities were reported.
	3-6 mg	50 (26 melatonin, 24 placebo)	Mean scores of side effects based on the stimulant drug side effects questionnaire were 11.35±8.81 in melatonin and 10.16±9.05 in placebo group (not statistically significant difference, P=0.686).
	3 or 6 mg	50 (26 melatonin, 24 placebo)	
	2.5-10 mg	45	The most remarkable AE was worsening of seizure activity following treatment with high doses of melatonin (10 mg) in 1 participant with autism spectrum disorder who was also taking dexamphetamine and sodium valproate, although seizure control returned back to normal after stopping melatonin.
	2-5 mg	125 (60 melatonin, 65 placebo)	The paediatric prolonged-release formulation of melatonin was generally safe; somnolence was more commonly reported with melatonin than placebo. During the double-blind phase, severe events were reported by 13 (21.7%) participants in the melatonin and 13 (20.0%) participants in the placebo group, with similar patterns. One patient in the melatonin group

[redacted]			discontinued due to non-serious AEs (fatigue, agitation and stereotypy). One patient in the placebo group temporarily discontinued due to 2 SAEs (pneumonia and respiratory tract infection viral) and 1 non-serious AE (tachypnea). There were no notable differences between melatonin and placebo for mean changes in BP, pulse rate, respiratory rate or temperature.
	1-5 mg	74	Treatment was well-tolerated. No side effects related to melatonin were reported.
	1-4 mg	99	Treatment-emergent AEs did not occur subsequent to week 16 after medication onset and the neuro-developmental disorders did not deteriorate in follow-up phase.

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; AE, adverse event; BP, blood pressure; SAE, serious adverse event

In general, several clinical studies, in which melatonin (at doses ranging from 0.5 to 6 mg) was administered to children and/or adolescents for periods of up to 3 years, have reported safety data, though none was specifically designed as safety study. Serious AEs or other important safety signals were not observed, though the safety data comprised primarily AEs reported by patients or their parents/caregivers or collected on questioners by the investigators. None of the studies systematically measured routine blood chemistry or haematology parameters. The lack of data for endocrine parameters and for reproductive issues in general could be of value, considering the apparent role of endogenous melatonin, more specifically the gradual fall in melatonin level around 9-10 years of age, in the cascade of events preceding the awakening of the hypothalamic-pituitary-gonadal axis at puberty [redacted]

2.5.5.1.3 Safety in special populations

Fertility and reproduction

In man, there is evidence that changes in melatonin secretion by the pineal gland can modulate the activity of the reproductive neuroendocrine axis. Indeed, the results of several studies have shown the clear correlation between melatonin and gonadotropins and/or sexual steroids, which suggest that melatonin may be involved in the sexual maturation, ovulation or menopause. Decreased secretion of melatonin which coexists with increased fertility in the summer is specific for women living on the north hemisphere. Moreover, abnormal levels of melatonin in blood are associated with several disorders of the hypothalamus-pituitary-gonads axis activity, i.e., precocious or delayed pubertas, hypogonadotrophic or hypergonadotrophic hypogonadism, or amenorrhoea. Melatonin binding sites have been demonstrated in the CNS (mainly in the arterior lobe or else *pars dystalis* of the pituitary and hypothalamic SCN) as well as in the reproductive organs, e.g., human granulosa cells, prostate and spermatozoa. Therefore, melatonin can influence the gonadal function indirectly, via its effect on gonadotropin-releasing hormone (GnRH) and/or gonadotropins secretion, as well as directly; several data show that melatonin can be synthesised in gonads [redacted]. Infertility treatments are associated with significant levels of reactive oxygen species which have the potential to negatively affect the quality of oocytes and embryos. Based on recent data, melatonin shows promising effects as an adjunctive therapy in the treatment of infertility due to its unique antioxidative characteristics and safety profile. Melatonin is also a key factor in the regulation of seasonal variation in gonadal activity. The circadian disturbances related to reproduction are probably subsequent to the seasonal change. Moreover, melatonin might also be considered essential for both spermatogenesis and folliculogenesis. Exposure to bright light, suppressing the concentration of melatonin in circulation, is considered to be useful in the treatment of both male and female infertility in

couples with abnormal melatonin metabolism [redacted]

Male reproductive toxicity: Constant short photoperiod has been shown to cause gonadal arrest and reduction in the transcriptional activity of the cAMP responsive element modulator (CREM) gene in hamsters [redacted] A number of early studies have examined the influence of exogenous melatonin on pulsatile LH, diurnal rhythm of testosterone and endogenous melatonin profile.

[redacted] evaluated the responses of LH, FSH, prolactine, thyroid-stimulating hormone (TSH), cortisol and aldosterone to a stimulation test with GnRH, thyrotrophin-releasing hormone (TRH), ACTH and testosterone to human chorionic gonadotrophin (hCG), along with the serum levels of the thyroid hormones triiodothironine (T_3) and T_4 in 6 healthy adult men. Such measurements were repeated after a 2-month course of oral treatment with melatonin 2 mg/day at 18:00. After treatment, a marked elevation of mean serum melatonin levels was recorded with a significant phase-advance of its circadian rhythm. The 24-h patterns of cortisol and testosterone displayed an anticipation of the morning acrophase of ~1.5 h (not significant) for cortisol and 3 h ($P<0.05$) for testosterone. Prolactin pattern and serum levels of thyroid hormones were unchanged. Also, circadian organisation of the cardiovascular variables did not show any changes following melatonin supplementation; the pituitary, adrenal, and testicular responses to specific stimuli were comparable prior to and after treatment. These results are compatible with the view that the melatonin signal may provide temporal cues to the neuroendocrine network for the organisation of testicular circadian periodicity.

Further data have indicated that an evening melatonin administration (3 mg) decreases the next-day LH secretion in normal adult males without altering testosterone levels or the endogenous nocturnal melatonin secretory pattern [redacted] Subsequent study results have suggested that long-term melatonin administration (6 mg, every evening for 1 month) does not alter the secretory patterns of reproductive hormones in normal men [redacted]

Anderson and colleagues recruited a total of 12 healthy adult men to investigate the effect of exogenous melatonin on the sensitivity of the hypothalamo-pituitary axis to sex steroid negative feedback, in a double-blind, randomised crossover trial. Daily treatment with melatonin (100 mg orally, at 16:00 h, for 14 days) resulted in persistently high circulating levels of the hormone for 14 days. This treatment had no significant effect on the secretion of LH, FSH, prolactin or testosterone based on the first week of each study (melatonin compared with placebo). Administration of testosterone propionate (intramuscular injection) caused a rapid 3- to 4-fold increase in testosterone plasma concentrations which was at a maximum at 8 h and had returned to baseline within 4 days, with a similar pattern in both the melatonin and placebo periods [redacted]

Later studies suggest that restoration of long photoperiod may result in recovery of spermatogenesis. This modulation is dependent on the photoperiod, associated with the change in melatonin production and can be reproduced by artificial lighting. Melatonin may be involved in the regulation of spermatogenesis or oogenesis during development and act as the hormonal messenger whose function would be to connect germ cells and Sertoli or follicular cells, respectively [redacted] Hence, it may also contribute to the

improvement of male reproductive health and potential (particularly extrapineally-produced melatonin), protecting against several kinds of testicular injuries mainly through its antioxidant capacities [redacted]

Female reproductive toxicity: Although melatonin levels vary significantly between night and day shift workers, LH and FSH levels do not; this suggests that the menstrual irregularity associated with shiftwork could be explained by melatonin fluctuations. These findings are in line with the above-mentioned central effects on the HPA system, being capable of modifying the release of gonadotrophins and GnRH [redacted] Early data indicate that an enhancing effect of melatonin on the LH and FSH responses to submaximal GnRH stimuli is evident in the follicular, but not the luteal, phase of the menstrual cycle and infer an endocrine window for the effect of melatonin on gonadotropin secretion [redacted]. Moreover, the circadian misalignment caused by shift work affects fertility and the fetus, increasing the risk of miscarriage, premature birth and low birth weight, phenomena observed in night workers [redacted] At very high doses, when combined with progesterone, melatonin has the ability to suppress ovulation in humans, possibly by interfering with LH release [redacted] This may represent an evolutionary remnant with inhibition of ovulation during darker months designed to prevent the birth of offspring when resources are less abundant.

Melatonin is also considered to delay the ovarian aging due to its cytoprotective actions as an antioxidant [redacted] Indeed, in both animal models and women, melatonin supplementation suggests a therapeutic and preventative potential, which may be attributed mainly to its antioxidant properties and action as hormone modulator. Short-term supplementation stydies of up to 6 months suggest that a daily posology of 2-18 mg of melatonin may have the potential to improve fertility rate, oocyte quality, maturation and number of embryos. However, the evidence available so far on the effects of melatonin supplementation covering gestational age and gestational outcomes is very scarce, requiring further research [redacted]

Early studies have shown that exogenous melatonin has a stimulatory effect on prolactin release without affecting the temporal pattern of its pulsatile secretion in normal women. Melatonin has minor, if any, effect on TSH secretion whereas the effect on LH may depend on individual sensitivity [redacted]. In a short-term pilot study, in which 22 insomniac patients (6 mean and 16 women; mean±SD age: 60.1±9.5 years; some also taking benzodiazepines) received 3 mg of (oral) melatonin daily for 6 months, serum prolactin, FSH, TSH or oestradiol levels did not show changes after 6 months [redacted]

An early study has presented some data related to the influence of melatonin or melatonin-progestin combinations on the pituitary-ovarian axis and ovulation in 32 women. Melatonin was administered at the dose of 300 mg to 12 women for 4 months, particularly, to 8 women daily (days 1-30) and to 4 women on days 5-17 of the cycle. A combination of melatonin plus the synthetic progestin norethisterone (NET) was given to 16 women, on days 1-21, at melatonin/NET dosages of 300/0.75, 75/0.75, 7.5/0.75 and 75/0.30 mg. In addition, 2 women received 300 mg melatonin alone and 2 were given 300 mg melatonin with 0.15 mg NET on days 1-21 for 2 months. After 4 months, daily administration of 300 mg melatonin (days 1-30)

caused significantly decreased mean LH levels compared to those in 8 non-treated controls ($P<0.001$). In addition, compared to the control data, a significant inhibition of progesterone in the 1st and 4th medication months ($P<0.001$) was observed. LH and oestradiol inhibition reached significance in the 4th month of treatment ($P<0.005$). Also, the treatments of 300 mg (days 5-17) and 75 mg melatonin combined with 0.3 mg NET caused a significant decrease in LH, oestradiol and progesterone levels compared to those in the control group in the 1st and 4th months ($P<0.05$). The data further suggest an additive or synergistic effect between melatonin and NET. The medications did not alter sleep-wake rhythms and were not complicated by any AEs [redacted]

Taking the above data into consideration, administration of exogenous melatonin is not recommended in women and men planning pregnancy. This is also in line with the corresponding recommendations of the SmPCs of other marketed melatonin medicinal product formulations for oral use.

Pregnancy

The role of melatonin in embryofetal development has been recently reviewed by [redacted] The pineal gland develops completely postpartum thus, both the embryo and the fetus are dependent on the maternal melatonin provided transplacentally. Melatonin appears to be involved in the normal outcome of pregnancy beginning with the oocyte quality and finishing with the parturition. Its pregnancy night-time concentrations increase after 24 weeks of gestation, with significantly high levels after 32 weeks. MTs are widespread in the embryo and fetus since the early stages. There is solid evidence that melatonin is neuroprotective and has a positive effect on the outcome of compromised pregnancies. In addition, chronodisruption leads to a reproductive dysfunction and appears to be a key contributor to offspring diseases that develop in adult life. Melatonin decreases in conditions associated with serious outcome for the fetus and seems to be involved in pre-eclampsia and intrauterine growth restriction [redacted]. Indeed, it has been suggested that exogenous melatonin increases glutathione peroxidase activity in the chorion and thereby may protect indirectly against free radical injury and thus it could be useful in treating pre-eclampsia and possibly other clinical states involving excessive free radical production, such as intrauterine fetal growth retardation and foetal hypoxia [redacted]

Melatonin treatment during human normal or abnormal pregnancy has been studied for a large range of conditions and at different times during the gestational period. Melatonin administration started prior to IVF-cycles, continued during pregnancy and was associated with improved pregnancy outcomes [redacted]. In addition, it appears that the fetuses' sleep patterns develop in the late pregnancy, melatonin being the regulating factor. A normal sleep pattern is involved in the neurodevelopment and there is solid evidence that melatonin is involved in fetal neuroprotection [redacted] Thus, the influence of melatonin on the developing human fetus may not be limited to entertaining the circadian rhythmicity. Alterations in maternal or placental melatonin might alter fetal melatonin levels and thus, gene expression in the fetal nervous system [redacted]

Melatonin crosses the placenta in humans. Therefore, it is likely, if taken by pregnant women, that the fetus will be exposed to melatonin, and the possibility exists that it will modify

subsequent development in terms of the circadian system and the timing of puberty [redacted]

Overall, since there are no or limited amount of data for the use of melatonin in pregnant women and according to SmPCs of other marketed melatonin oral formulation products, melatonin is not recommended during pregnancy or in women of childbearing potential not using contraception.

Lactation and breastfed infants

Melatonin is a normal component of breast milk, with concentrations higher during night- (with a peak around 03:00) than daytime [redacted] Elective caesarean section results in higher daytime colostrum levels than with vaginal delivery [redacted] Some authors suggest that mothers should nurse in the dark at night in order to avoid reductions in the melatonin content of breast milk, which could disturb infant sleep patterns [redacted] Differentiating milk pumped during the day from milk pumped during darkness has also been suggested for women pumping milk for their infants [redacted] Some studies have attributed longer sleep time in breastfed infant to the presence of melatonin in breast milk [redacted]. Another study found higher colostrum melatonin levels at night which appeared to increase the phagocytic activity of colostral cells against bacteria [redacted] Exogenous administration of melatonin has no specific use during breastfeeding; no data exist on the safety of maternal use of melatonin during breastfeeding. However, doses higher than those expected in breastmilk after maternal supplementation have been used safely in infants [redacted] It is unlikely that short-term use of usual doses of melatonin in the evening by a nursing mother would adversely affect her breastfed infant, although some authors recommend against its use in breastfeeding due to the lack of data and a relatively long t½ in preterm neonates [redacted]

As mentioned, melatonin exhibits a circadian rhythm in body fluids. A study conducted by [redacted] determined whether melatonin is detectable in human milk and, if so, whether it exhibits a daily rhythm. Blood and milk were sampled between 14:00 and 17:00 and again between 02:00 and 04:00 from 10 mothers 3-4 days after delivery. Melatonin in both fluids was beyond the limit of detection during the day, whereas during the night, its concentration was 280±34 pmol/L in serum and 99±26 pmol/L in milk. Six mothers collected milk after each feeding throughout one 24-h period within 3 months after delivery. Melatonin in the milk of all subjects exhibited a pronounced daily rhythm, with high levels during the night and undetectable levels during the day. The presence of the rhythm in milk suggests that melatonin fluctuations in milk might communicate the time of day to breastfed infants.

Available PD/toxicological data in animals have shown excretion of melatonin metabolites in milk (please refer to Module 2.4 Non Clinical Overview). A risk to the suckling child cannot be, thus, excluded. As per the proposed SmPC, melatonin 1 mg/ml oral solution should not be used during breastfeeding.

2.5.5.2 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTION

The potential PD and PK interactions between melatonin and other substances have been investigated and presented in all approved PI texts of melatonin-containing medicinal products (tablets and oral solutions). The most important issues stated in the following subsections are based on either drug interaction in clinical studies or literature data on potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified with contraindicated drugs).

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

2.5.5.2.1 Pharmacodynamic drug interactions

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

Anticoagulants: An early Cochrane review on melatonin for the prevention and treatment of jet lag by [redacted] described 6 cases of adverse drug reactions (reported by the WHO Uppsala Monitoring Centre database), all suspected to be due to interaction with warfarin. Both drugs were administered concurrently for 5-8 days. In 3 cases, an increased prothrombin time (PT) was demonstrated with bleeding events (eye haemorrhage, purpura and nose bleeding), whereas the 3 other cases reported decreased PT. Some previous case reports have shown that melatonin is associated with decreased PT with no evidence of clotting; however, in these cases some bleeding complications were noted [redacted]. A later case series study has evaluated the potential drug interaction between these drugs, including 10 patients who had changes in the international normalised ratio (INR) and PT while receiving concurrently warfarin and (one dose of) melatonin during their hospital stay (2-10 days). Melatonin dose was stable in all 10 patients while the dose of warfarin was either increased or decreased in some patients. Both INR and PT increased in most patients during concurrent treatment, with no bleeding events being noted. After calculation of the drug interaction probability scale (DIPS) score for each patient, it was found that 6 patients experienced possible drug interaction, 2 had probable drug interaction and 2 had doubtful drug interaction [redacted]

An explanation for this interaction is that melatonin is metabolised by CYP450 in the liver [redacted], including primarily CYP2C19 and CYP1A families (particularly CYP1A2) and possibly CYP2C9 [redacted] Melatonin appears to inhibit CYP1A2 [redacted] and induce CYP3A. Theoretically, when melatonin is administered concomitantly with drugs metabolised by these isoenzymes, this might inhibit the

metabolism of these drugs, resulting in increased serum levels. Warfarin is metabolised primarily by CYP2C9 as well as by CYP2C19, CYP2C8, CYP2C18, CYP1A2, and CYP3A4, to inactive metabolites. The (*R*)-enantiomer of warfarin is metabolised by CYP1A2, while the (*S*)-enantiomer by CYP2C9; however, the latter has been determined to possess the major pharmacological activities of racemic warfarin [redacted]

Overall, since the concurrent use of melatonin and warfarin may result in INR and PT changes and affect coagulation activity, caution is advised when using melatonin together with anticoagulant agents, including warfarin, coumarin-analogues, as well as novel direct-acting anticoagulants [redacted], as melatonin may enhance the effect of these drugs resulting in increased risk of bleeding. In addition, monitoring INR and PT regularly is recommended when both medications are administered together.

Benzodiazepines: As both melatonin and benzodiazepines bind $GABA_A$ receptors, there is a potential for PD interaction with benzodiazepines [redacted]

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

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

Nifedipine: Melatonin may reduce the hypotensive effect of nifedipine, so caution should be exercised in this combination and dose adjustment of nifedipine may be needed [redacted]

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

Zaleplon, zolpidem, zopiclone: Melatonin may enhance the sedative properties of benzodiazepine and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical study, there was clear evidence of a transient PD interaction between melatonin prolonged-release tablet and zolpidem 1 h after concomitant dosing. Concomitant administration led to an increased reduction in attention, memory and coordination compared to zolpidem alone [redacted]

Furthermore, adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, tryptophan and alcohol affect the endogenous secretion of melatonin in the epiphysis. Whether these interactions are of clinical significance is unknown [redacted]

2.5.5.2.2 Pharmacokinetic drug interactions

Possible interactions of melatonin with concurrently administered drugs were investigated in *in vitro* studies utilising human hepatic post-mitochondrial preparations; similar studies were conducted with rat preparations to ascertain whether rat is a suitable surrogate for human. Drugs were selected based not only on the knowledge that the 6-hydroxylation of exogenous melatonin, its principal pathway of metabolism, is mainly mediated by hepatic CYP1A2, but also on the likelihood of the drug being concurrently administered with melatonin. Hepatic preparations were incubated with either melatonin or 6-hydroxymelatonin in the presence and absence of a range of concentrations of interacting drug, and the production of 6-sulphatoxymelatonin monitored using a radioimmunoassay procedure. Of the drugs screened, only the potent CYP1A2 inhibitor 5-methoxypsoralen (MOP) impaired the 6-melatonin hydroxylation 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 to 6-sulphatoxymelatonin at concentrations attained following therapeutic administration. 17-Ethinhyloestradiol appeared not to suppress the 6-hydroxylation of melatonin but inhibited the sulphation of 6-hydroxymelatonin, but this is unlikely to result in an interaction following therapeutic intake of the steroid. Species differences in inhibition of melatonin metabolism in human and rat hepatic post-mitochondrial preparations were evident implying that the rat may not be an appropriate human surrogate in such studies [redacted]

Caffeine: Concomitant consumption of caffeine whose metabolism is principally catalysed by CYP1A2, more than doubled plasma levels and increased the bioavailability of melatonin, by impairing its presystemic metabolism [redacted]

Carbamazepine: CYP1A2 inducers, such as carbamazepine, may reduce melatonin plasma concentration [redacted]

Cigarette smoking: Exogenous serum melatonin levels were suppressed by smoking, especially when the levels of the hormone were high. Polycyclic aromatic hydrocarbons, a class of carcinogenic compounds present in tobacco, up-regulate CYP1A2 expression leading to accelerated melatonin metabolism [redacted]

CYP substrates: Increased CYP1A2 activity will lead to lower plasma levels and *vice versa*. For example, plasma melatonin levels were increased following fluvoxamine (a potent

inhibitor of CYP1A2 and to a lesser extent of CYP2C19) administration, presumably by impairing its CYP-mediated metabolism. Moreover, drugs that are CYP2C19 substrates, such as fluvoxamine, quinolones, cimetidine, 5- and 8-MOP, omeprazole, lansoprazole and citalopram, increased the urinary excretion of 6-sulphatoxymelatonin in individuals receiving exogenous melatonin; presumably these compounds decrease the CYP219-mediated metabolism of melatonin to acetylserotonin [redacted] Co-administration of melatonin with CYP1A2 inducers, such as carbamazepine, rifampicin and phenytoin, may result in reduced melatonin exposure through an increase in melatonin metabolism [redacted]

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

Antidepressants: Fluvoxamine is known to inhibit CYP1A2 potently, and to some extent also CYP2C19, whereas citalopram is without such an effect. Also, CYP enzymes are involved in the hepatic metabolism of melatonin. Fluvoxamine has been shown to increase serum levels of orally administered melatonin (17-fold higher AUC and 12-fold higher C_{max}) [redacted] Hence, this combination should be avoided.

Oestrogens: Melatonin downregulates the circulating levels of gonadal oestrogens and acts as an antioestrogen with mechanisms of action different to those of the commercially available antioestrogens and inhibits aromatase expression in human breast cancer cells. The metabolism by CYP1A1 isoenzymes is inhibited and CYP1A2 increases melatonin levels [redacted] Caution should be exercised in patients on oestrogens, e.g., oral contraceptives (OCs) or hormone replacement therapy, which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2 [redacted]. The effect of OCs on melatonin metabolism was studied in 29 subjects genotyped for CYP1A2 SNP g.-163C>A polymorphism. Plasma melatonin and 6-hydroxymelatonin concentrations were measured after a 6-mg melatonin dose. The mean melatonin AUC and C_{max} values were 4- to 5-fold higher in OC users than in non-OC users ($P<0.0001$), whereas the weight-adjusted clearance was significantly lower in OC users ($P<0.0001$). No significant difference in melatonin PKs between the genotypes and no additional effect by the genotype on the OC-induced increase in melatonin exposure were evident. Melatonin exposure had no significant effect on the state of alertness of the subjects. Overall, a significant inhibitory effect of OCs on CYP1A2-catalysed melatonin metabolism was seen; thereby, OC use can alter CYP1A2-phenotyping results [redacted]

2.5.5.3 UNDESIRABLE EFFECTS

As presented and discussed in the Section *'2.5.5.1 Toxicity'* of the current 2.5 Clinical Overview, drowsiness/sleepiness, headache and dizziness/disorientation are the most frequently reported AEs of melatonin dosing on a short-term basis to treat jet lag. Drowsiness, headache, dizziness and nausea are also the adverse reactions reported most frequently when typical clinical doses of melatonin have been received for periods of several days to several weeks by healthy persons and patients.

Within the following Table, adverse reactions to oral administration of melatonin (in the form of film-coated tablets and oral solutions) generally reported in clinical trials [redacted] or spontaneous case reports (e.g., [redacted] are listed, as reported in already [redacted]

These AEs are ranked under the MedDRA frequency classification: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data) *(MedDRA Introductory Guide, 2022)*.

Table 23. Tabulated list of AEs recorded in clinical trials, spontaneous case reports as well as postmarketing data after oral melatonin administration. Within each frequency group, undesirable effects are presented in the order of decreasing seriousness.

System Organ Class	Frequency	Effect
Infections and infestations	Rare	Herpes zoster
Blood and lymphatic system disorders	Rare	Leukopenia; thrombocytopenia.
Immune system disorders	Not known	Hypersensitivity reaction
Metabolism and nutrition disorders	Rare	Hypertriglyceridaemia
	Not known	Hyperglycaemia
Psychiatric disorders	Uncommon	Irritability; nervousness; restlessness; abnormal dreams; anxiety.
	Rare	Mood altered; aggressive behaviour; disorientation; libido increased; depressed mood; depression.
Nervous system disorders	Common	Headache; somnolence.
	Uncommon	Migraine; lethargy; psychomotor hyperactivity; dizziness.
	Rare	Syncope (fainting); memory impairment; restless legs syndrome; disturbance in attention; poor quality sleep; paraesthesia.
	Not known	Drowsiness; sedation.
Eye disorders	Rare	Visual acuity reduced; vision blurred; lacrimation increased.
Ear and labyrinth disorders	Rare	Vertigo positional; vertigo.
Cardiac disorders	Rare	Angina pectoris; palpitations.
Vascular disorders	Uncommon	Hypertension
	Rare	Hot flushes
Gastrointestinal disorders	Uncommon	Abdominal pain; upper abdominal pain; dyspepsia; oral ulcers; dry mouth; nausea.
	Rare	Gastro-oesophageal reflux disease; GI disorder; oral mucosal blistering; tongue ulceration; GI upset; vomiting; bowel sounds abnormal; flatulence; salivary hypersecretion; halitosis; gastritis.
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis; night sweats; pruritus; rash; dry skin.
	Rare	Eczema; erythema; hand dermatitis; psoriasis; rash generalised; rash pruritic; nail disorder.
	Not known	Tongue oedema; oedema of the oral mucosa.
Musculoskeletal and connective tissue disorders	Uncommon	Pain in extremity
	Rare	Arthritis; muscle spasms; neck pain; night cramps.
Renal and urinary disorders	Uncommon	Glycosuria; proteinuria.
	Rare	Polyuria; haematuria.
Reproductive system and breast disorders	Uncommon	Menopausal symptoms
	Rare	Priapism; prostatitis.
	Not known	Galactorrhoea
General disorders and administration site conditions	Uncommon	Chest pain; malaise.
	Rare	Fatigue; pain; thirst.
Laboratory and other examinations	Uncommon	Liver function test abnormal; weight increased.

System Organ Class	Frequency	Effect
	Rare	Hepatic enzyme increased; blood electrolytes abnormal.

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

Paediatric population

In the paediatric population, a low frequency of generally mild AEs has been reported. The number of AEs did not differ significantly between children who received placebo and children who received melatonin. The most common AEs were headache, hyperactivity, dizziness and abdominal pain. No serious AEs have been observed.

2.5.5.4 OVERDOSE

Symptoms

The most commonly reported signs and symptoms of overdose with oral melatonin are drowsiness, headache, dizziness and nausea. Ingestion of daily doses of up to 300 mg of melatonin did not cause clinically significant adverse reactions [redacted]. Flushes, abdominal cramps, diarrhoea, headache and scotoma lucidum have been reported after ingestion of extremely high melatonin doses (3-6 g) for several weeks.

Management

In case of an overdose, general supportive measures should be employed. Gastric lavage and administration of activated charcoal can be considered. The management measures (gastric lavage, activated charcoal, supportive measures based on symptoms) are generally acknowledged and have to be applied based on each case characteristics. Obviously, the larger the ingestion, the more aggressive measures may have to be taken at an emergency department [redacted]. Clearance of melatonin is expected within 12 h of ingestion [redacted]

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 THERAPEUTIC CONTEXT

2.5.6.1.1 Disease or condition

Jet lag

Each year millions of travelers undertake long distance flights over one or more continents. These multiple time zone flights produce a constellation of symptoms known as jet lag. The most important jet lag symptoms are due to disruptions to the body's sleep/wake cycle. Jet lag is therefore a syndrome associated with long-haul flights across several time zones, characterised by sleep disturbances, daytime fatigue, reduced performance, GI problems, loss of mental efficiency, weakness, irritability and generalised malaise. As with most syndromes, not all of the components must be present in any one case. Jet lag affects most air travelers crossing ≥5 times zones; the incidence and severity of jet lag increase with the number of time zones crossed. Westward travel causes less disruption than eastward travel as it is easier to lengthen, rather than to shorten, the natural circadian cycle. The sleep loss caused by the travel itself often contributes to jet lag. Clinical and pathophysiological studies also indicate that jet lag can exacerbate existing affective disorders. It has been suggested that dysregulation of melatonin secretion and occurrence of circadian rhythm disturbances may be the common links which underlie jet lag and affective disorders [redacted]

ADHD

ADHD is commonly associated with disordered or disturbed sleep. Evidence from published studies comparing sleep in individuals with ADHD with typically developing controls is most concordant for associations of ADHD with hypopnoea/apnoea and peripheral limb movements in sleep or nocturnal motricity in polysomnographic studies, increased sleep onset latency and shorter sleep time in actigraphic studies, bedtime resistance, difficulty with morning awakenings, sleep onset difficulties, sleep-disordered breathing, night awakenings and daytime sleepiness in subjective studies. Psychostimulant medications, such as methylphenidate, which are widely regarded as first-line therapy for ADHD, are associated with disrupted or disturbed sleep to as high as 80% of children with ADHD manifesting these difficulties [redacted]

SWD

SWD is characterised by excessive sleepiness and/or sleep disruption for ≥1 month in relation with the atypical work schedule. Individual tolerance to shift work remains a complex problem that is affected by the number of consecutive work hours and shifts, the rest periods and the predictability of work schedules. Sleepiness usually occurs during night shifts and is maximal at the end of the night [redacted] Night-shift work is associated with suppression of melatonin production, especially among fixed night-shift workers [redacted] Several studies have indicated that both melatonin production and sleep patterns are altered in shift workers. An alteration of the melatonin profile was seen in some shift workers, while in others,

it was found to be indistinguishable from those seen in day-shift workers [redacted]

2.5.6.1.2 Current therapies

Jet lag

A number of pharmacological interventions have been tried to minimise the effects of jet lag. Current therapies for short-term treatment of jet lag in adults include light therapy, melatonin, MT receptor analogues (ramelteon, agomelatine, tasimelteon), non-benzodiazepine hypnotics, caffeine, diphenhydramine and CNS stimulants. The patient's flight schedule, physical condition and individual response to treatment all play important role. Administering exogenous melatonin in the conventional afternoon to evening hours of a 24-h day promotes a phase shift in circadian rhythm and thus promotes sleep [redacted]

Insomnia in ADHD

Treatment of insomnia should always start with sleep hygiene education and optimising the stimulant or non-stimulant treatment of ADHD. Careful titration of stimulants and psychoeducation around sleep optimisation can improve the quality of sleep, possibly due to improved daytime structure, the maintenance of regular physical activity and improved mood [redacted]. Also, published guidelines of medical organisations, associations and institutions have stated the probable usefulness of melatonin for the treatment of sleep disturbances in ADHD. The Updated European Consensus Statement on the diagnosis and treatment of adult ADHD (2019) mentions that in children with ADHD and chronic insomnia, melatonin has been shown to advance the sleep onset and increase sleep duration [redacted] The Canadian Pediatric Society (2012) mentions that melatonin treatment for certain sleep problems in children and adolescents can be useful in special populations. Moreover, in EU/UK, the use of melatonin to treat sleep disorders in children and adolescents with ADHD is already approved in registered liquid melatonin products.

SWD

Published guidelines of medical organisations, associations and institutions have stated the potential usefulness of melatonin for the management of SWD in adults. The American Academy of Sleep published in 2007 a guideline for the Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders stating that melatonin use prior to daytime sleep is indicated to promote daytime sleep among night shift workers [redacted] In addition, the British Association for Psychopharmacology published an updated consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders [redacted] stating that adequate evidence exists on the efficacy of melatonin in irregular sleep wake rhythm or in SWD, including though some reports on the use in shift workers with varying results. The usefulness of melatonin in shift-work sleep disorder is also confirmed by the inclusion of this specific indication in other EU marketed melatonin oral formulations.

2.5.6.2 BENEFITS

Melatonin is remarkably effective in preventing or reducing jet lag and SWD in adults and in treating insomnia in children with ADHD and has been the subject of many studies. The overall presented results of the most representative available trials as tabulated and discussed within Section *'2.5.4 Overview of Efficacy'* of the current Clinical Overview successfully justify the claimed indications and posology regimens referring to the proposed melatonin oral solution formulation for the intended population groups.

2.5.6.3 RISKS

Melatonin is well-tolerated with a good safety profile, with most AEs being of mild severity. Adverse reactions due to melatonin use are minimal at the low doses received for the short duration proposed. They may include somnolence, headaches, nausea, diarrhoea, abnormal dreams, irritability, nervousness, restlessness, insomnia, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, hypertension, abdominal pain, heartburn, mouth ulcers, dry mouth, hyperbilirubinaemia, dermatitis, night sweats, pruritus, rash, dry skin, pain in the extremities, symptoms of menopause, chest pain, glycosuria, proteinuria, abnormal liver function tests, increased weight, tiredness, mood swings, aggression and feeling hungover. Its use is not recommended during pregnancy or breastfeeding and in the paediatric population of 0-6 years old [redacted].

2.5.6.4 BENEFIT-RISK ASSESSMENT

The current Clinical Overview refers to a medicinal product containing melatonin as an active substance in the form of oral solution, intended for oral administration, at the strength of 1 mg/ml. The relevant Marketing Authorisation Application that is subject of this Expert Report is submitted under Article 10.a of Directive 2001/83/EC, as amended (WEU application). According to Article 10.a of Directive 2001/83/EC as amended, '*the Applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substance(s) of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety*'. In that event, the test and trial results are replaced by appropriate scientific literature.

Melatonin is a member of the class of acetamides and a member of tryptamines. In vertebrates, besides being produced in peripheral tissues and acting as an autocrine and paracrine signal, melatonin is centrally synthetised by a neuroendocrine organ, the pineal gland. Independently of the considered species, pineal hormone melatonin is always produced during the night and its production and secretory episode duration are directly dependent on the length of the night. As its production is tightly linked to the light/dark cycle, melatonin main hormonal systemic integrative action is to coordinate behavioural and physiological adaptations to the environmental geophysical day and season. The circadian signal is dependent on its daily production regularity, on the contrast between day and night concentrations and on specially developed ways of action. During its daily secretory episode, melatonin coordinates the night adaptive physiology through immediate effects and primes the day adaptive responses through prospective effects that will only appear at daytime, when melatonin is absent. Similarly, the annual history of the daily melatonin secretory episode duration primes the CNS/endocrine

system to the following seasons. Remarkably, maternal melatonin programs the fetuses' behaviour and physiology to cope with the environmental light/dark cycle and season after birth. These unique ways of action turn melatonin into a biological time-domain–acting molecule.

Melatonin is involved in numerous biological functions including synchronising circadian rhythms, such as sleep-wake timing and blood pressure regulation, the stress response, aging, immunity and the control of seasonal rhythmicity including reproduction, fattening, moulting and hibernation. Many of its effects are through activation of the MT receptors, while others are due to its role as an antioxidant. The therapeutic role of melatonin is clinically significant and well-established within the EU/UK. Also, large clinical trials proving the efficacy of melatonin-containing products are present in published literature. Its pharmacology, toxicology and PKs have been fully characterised through systemic routes of administration since decades.

The requirements of the legal basis selected for submission include, within robust literature data, string evidence of the well-established use of the active substance within the Community for the intended indications in the intended target age population groups for more than 10 years. There is a variety of indications, regarding sleep disorders and circardian rhythms, currently approved for the oral solid and liquid melatonin formulations (IR, controlled-released, SR) in EU. A number of RCTs has been conducted aiming to investigate the efficacy and safety of melatonin treatment for the proposed indications in adults, adolescents and paediatric patients aged ≥6 years. These clinical studies involve heterogenous population groups (targeted to the therapeutic indications) as well as different oral melatonin doses/formulations, compared to other medication or placebo. In this respect, all relevant published data have been critically reviewed within the scope of the present Clinical Overview. The pharmacology, PDs and PKs, as well as efficacy and safety of melatonin have been fully reviewed and the role of melatonin as an oral therapeutic agent can be considered well-established within the EU/UK, being in clinical practice far more than 10 years.

Furthermore, in order to provide evidence that the proposed formulation is comparable to the already marketed products, aiming to claim similar efficacy and safety, a comparability exercise in terms of composition, quality, safety of excipients and their potential effects on absorption and bioavailability of oral melatonin have been thoroughly addressed. The oral solution medicinal product formulation under approval contains common inert excipients, widely used in pharmaceutical preparations and also contained in other EU/UK approved melatonin oral solutions, without any proven effect on drug local action, systemic bioavailability and safety also in the paediatric population. Furthermore, proprietary bridging documentation ensures that the new formulation is comparable in terms of efficacy and safety to the already existing oral melatonin products (solid and liquid dosage forms) in the EU/UK clinical practice as well as-by extrapolation- to those administered in the pivotal clinical trials of the literature and. Last but not least, the acceptable safety of excipients present in the formulation for the targeted paediatric population has been also evaluated and confirmed.

Concluding the above, the bibliographical data and the justifications presented in this Clinical Overview are considered to provide sufficient information for the successful submission of Melatonin 1 mg/ml oral solution under the Legal basis of Well-Established Use (Article 10.a

of Directive 2001/83/EC, as amended), for the claimed indications and the target age population groups. Therefore, no differentiation in the *in vivo* efficacy and safety profile is expected for the product under submission, compared to the already EU/UK authorised liquid and solid melatonin formulations or the products administered in the clinical studies presented in this Clinical Overview. The proposed strength is also approvable from a clinical point of view, in accordance with the proposed dosage regimens for the claimed indications and target populations.

2.5.7 LIST OF LITERATURE REFERENCES