RISK MANAGEMENT PLAN FOR SLENYTO

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Date for EU-RMP: 21 January 2025 Version 3.2

[redacted]

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse event
ANSM	National Agency for the Safety of Medicines
AS	Angelman Syndrome
ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Chemical (Classification)
EEC	European Economic Community
EU	European Union
FAS	Fetal Alcohol Syndrome
IMS	Intercontinental Marketing Statistics
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
NGD	Neurogenetic disorders
PD	Pharmacodynamics
PIL	Patient Information Leaflet
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
REM	Rapid Eye Movement
RMP	Risk Management Plan
RSI	Reference Safety Information
RTU	Temporary Registration Use
SMS	Smith-Magenis Syndrome
SmPC	Summary of Product Characteristics
SWS	Slow Wave Sleep
TS	Tourette's Syndrome
TSB	Bourneville tuberous sclerosis
TSC	Tuberous Sclerosis Complex
TSH	Thyroxine Stimulating Hormone

Note: The terms 'trial' and 'study' may be used interchangeably throughout.

Overview of EU-RMP versions:

RMP version to be assessed as part of this application:

RMP version number: 3.2

Data lock point for this RMP: 31 December 2023

Date of final sign-off: 21 January 2025

Rationale for submitting an updated RMP: Addition of a new indication for the treatment of insomnia in children and adolescents with attention deficit hyperactivity disorder.

Summary of significant changes in this RMP:

RMP PART/MODULE	Version number when last submitted / or Not Applicable	Date Last Updated for Submission
PART II SAFETY SPECIFICATION		
Module SI Epidemiology of the indication(s) and target population(s)	3.2	21 January 2025
Module SII Non-clinical part of the safety specification	3.1	21 November 2024
Module SIII Clinical trial exposure	3.0	21 May 2024
Module SIV Populations not studied in clinical trials	3.0	21 May 2024
Module SV Post-authorization experience	3.2	21 January 2025
Module SVI Additional European Union (EU) requirements for the safety specification	3.0	21 May 2024
Module SVII Identified and potential risks	3.0	21 May 2024
Module SVIII Summary of the safety concerns	1.6	22 November 2022
PART III PHARMACOVIGILANCE PLAN	1.6	22 November 2022
PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES	1.1	12 June 2018
PART V RISK MINIMIZATION MEASURES	1.6	22 November 2022
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	3.2	21 January 2025
PART VII ANNEX 2		
ANNEX 1 EudraVigilance Interface	1.0	13 March 2018
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study program	1.0	13 March 2018
ANNEX 3 Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan	1.0	13 March 2018
ANNEX 4 Specific adverse drug reaction follow-up forms	1.0	13 March 2018
ANNEX 5 Protocols for proposed and on-going studies in RMP part IV	1.1	12 June 2018
ANNEX 6 Details of proposed additional risk minimization activities (if applicable)	1.0	13 March 2018
ANNEX 7 Other supporting data (including referenced material)	1.0	13 March 2018
ANNEX 8 Summary of changes to the risk management plan over time	3.2	21 January 2025

Other RMP versions under evaluation:

RMP version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/004425/II/0025

Date of approval (opinion date): 25 July 2024

Name of EU Qualified Person for Pharmacovigilance (QPPV):

QPPV Name:	Graeme Ladds
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

PART I PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name):	Melatonin
Pharmacotherapeutic group(s) (ATC code):	N05CH01
Marketing Authorization Holder or Applicant:	RAD Neurim Pharmaceuticals EEC SARL
Medicinal products to which this RMP refers:	Slenyto 1 mg and 5 mg prolonged-release tablets.
Invented name(s) in the European Economic Area (EEA):	Slenyto
Marketing authorization procedure:	Centralized
Brief description of product including:	Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin.
Chemical class:	The Anatomical Therapeutic Chemical (ATC) classification is N05CH01: Nervous system, psycholeptics, hypnotics and sedatives, melatonin receptor agonists, melatonin.
Summary of mode of action	Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.
Important information about its composition	Slenyto 1 mg melatonin strength: Excipients include: Ammonio Methacrylate Copolymer Type B, Calcium Hydrogen Phosphate Dihydrate, Lactose Monohydrate, Colloidal Anhydrous Silica, Talc, Magnesium Stearate Film Coating: Carmellose sodium (E466), Maltodextrin, Glucose monohydrate, Lecithin (E322), Titanium dioxide (E171), Iron oxide red (E172), Iron oxide yellow (E172) Slenyto 5 mg melatonin strength: Ammonio Methacrylate Copolymer Type A, Calcium Hydrogen Phosphate Dihydrate, Lactose Monohydrate, Colloidal Anhydrous Silica, Magnesium Stearate

	Film Coating: Carmellose sodium (E466), Maltodextrin, Glucose monohydrate, Lecithin (E322), Titanium dioxide (E171), Iron oxide yellow (E172)
Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/slenyto-epar-product-information_en.pdf.
Indication(s) in the EEA:	
Current:	Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient.
Proposed:	Slenyto is indicated for: - treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient. - treatment of insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been insufficient.
Dosage in the EEA:	
Current:	The recommended starting dose is 2 mg of Slenyto. If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg. Slenyto should be taken once daily, 0.5-1 hour before bedtime and with or after food. Data are available for up to 2 years' treatment. The patient should be monitored at regular intervals (at least every 6 months) to check that Slenyto is still the most appropriate treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant

	treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment. If a tablet is forgotten, it could be taken before the patient goes to sleep that night, but after this time, no other tablet should be given before the next scheduled dose.
Proposed:	No changes proposed to current dosing regimen for insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings. **Insomnia in children and adolescents aged 6-17 years with ADHD** The recommended starting dose is 1-2 mg. The dose may be adjusted on an individual basis to 5 mg per day regardless of age of the child. If clinically needed, the maximum daily dose may be increased to 10 mg. The lowest effective dose should be taken for the shortest period. Slenyto should be taken once daily, 0.5-1 hour before bedtime and with or after food. After approximately 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be monitored regularly (at least every 6 months) to check that Slenyto 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 a year. If a tablet is forgotten, it could be taken before the patient goes to sleep that night, but after this time, no other tablet should be given before the next scheduled dose.

Pharmaceutical form(s) and strength(s):	
Current:	Prolonged release tablet. Slenyto 1 mg prolonged release tablets Pink, film-coated, round, biconvex, 3 mm diameter tablets with no imprint. Slenyto 5 mg prolonged release tablets Yellow, film-coated, round, biconvex, 3 mm diameter tablets with no imprint.
Proposed:	No changes proposed to current pharmaceutical form and strengths.
Is/will the product be subject to additional monitoring in the EU?	No

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATIONS

Indication approved with the initial Marketing Authorization: Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

Current indication: Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient.

Incidence: Pediatric insomnia in children and adolescents is a widespread problem. Unlike insomnia in the adult population, pediatric insomnia is often reported by a caregiver. Therefore, the subjective evaluation of poor quality of sleep lacks descriptive clinical detail and definition and is usually described as difficulty in falling asleep and/or staying asleep. In addition, young children tend to sleep longer than adults (Shi et al, 2013). Thus, although insomnia as a condition exists in children, the characteristic symptoms of insomnia, in particular total sleep time and quality of sleep may differ between the age groups (i.e., ≥ 55 years and ≤ 18 years).

Sleep disturbance in children with autistic spectrum disorder and/or neurogenetic disorders.

Sleep disturbance is one of the most common complaints in children with autism spectrum disorder, mental retardation, or other developmental delays (Krakowiak et al, 2008; Pillar et al, 2000, Souders et al, 2009). High prevalence for moderate sleep disturbances in these child populations are associated with significant sleep problems and subsequent distress for the families of these children, which in many cases, lead to the decision to institutionalize the children (Doo and Wing 2006). Sleep disturbances in children suffering from ASD and NGD are often severe and associated with sleep onset difficulties and disrupted sleep maintenance (Mindell et al, 2006).

Felder et al (2018) looked at the sleep burden placed upon mothers looking after children with Autism and although this did not result in any child being institutionalised the overall lack of or disturbed sleep for the carers did relate to health issues in the parents.

Specifically, a frequent cause of families giving up their care is discontinuous sleep with frequent awakenings throughout the night. There is a growing body of evidence on abnormal melatonin secretion in children with neurodevelopmental disorders (Phillips and Appleton 2004).

A review by Angriman et al, 2015 describes research in pediatric sleep disorders associated with neurodevelopmental disabilities (NDDs) and their treatment.

NDDs affect more than 2% of the general population and represent more than 35% of the total cases of children referred to a neuropsychiatric center for sleep problems. Specific clinical and therapeutic aspects of sleep disorders associated with Down syndrome, Fragile X syndrome, Prader–Willi syndrome, Angelman syndrome, Rett syndrome, Smith–Magenis syndrome, cerebral palsy, and autism spectrum disorders are described.

Furthermore, the drugs commonly used for sleep disorders in children with NDDs are described. The review clearly highlighted that children with NDDs are often affected by sleep disorders that require an appropriate clinical and therapeutic approach to improve quality of life in both patients and families.

Among the neuropsychiatric conditions associated with Tourette's Syndrome (TS), ADHD and Obsessive Compulsive Disorder (OCD) are widely accepted as genuine comorbidities ("the Tourette's syndrome triad") (Kurlan 2010). Sleep disorders were also reported to be not uncommon in patients with TS (Mol Debes et al, 2008; Comings and Comings, 1987; Ghosh et al, 2014; Cohrs et al, 2001).

In an early study, sleep disturbances occurred in 62% of patients with TS, and polysomnography study revealed sleep apnea, abnormal arousal pattern, and motor and vocal tics during all stages of sleep. Ghosh et al (2014) reported that 64% of TS patients have DSM-V coded sleep disorders.

Pelc et al (2008) provided a review of sleep problems associated with Angelman syndrome which is a neurogenetic condition characterized by developmental delay, absence of speech, motor impairment, epilepsy and a peculiar behavioral phenotype that includes sleep problems. It is caused by lack of expression of the UBE3A gene on the maternal chromosome 15q11-q13.

Sleep disturbances, abnormal sleep-wake cycles and a diminished need for sleep are included in the consensus guidelines for the diagnostic criteria of AS and are highly common in patients, especially in early childhood between 2-6 years of age (Williams et al., 1995; Williams et al., 2006; Shelton and Malow, 2021). Sleep problems in Angelman syndrome reflect abnormal neurodevelopmental functioning presumably involving dysregulation of GABA-mediated inhibitory influences in thalamocortical interactions. Management may be difficult, particularly in young children; it primarily involves behavioral approaches, though pharmacological treatment may be required.

Over 80% of individuals with Rett syndrome are affected by sleep disorders, which vary with age and mutation type (Young et al. 2007; Tascini et al. 2022). Impaired sleep pattern is included in the supportive criteria for Rett syndrome (Neul et al. 2010; Shelton and Malow 2021). Children with Rett syndrome have also been found to have impaired secretion of melatonin, leading to severe sleep problems (Miyamoto et al. 1999).

Sleep problems are common in TSC patients (Bruni et al. 1995) and are at least partially associated with significant differences in melatonin secretion profiles in TSC patients versus normal controls (Hancock et al. 2005). Consistently, melatonin release shift appears to depend on the number of seizures in patients (Paprocka et al. 2017).

In Williams syndrome, a high rate of sleep disturbances has been reported as early as 18 months old (Gwilliam et al. 2020; Shelton and Malow 2021). The sleep disturbances were reported together with a lower rise in melatonin levels before sleep compared to age-matched controls (Sniecinska-Cooper et al. 2015). As sleep disturbance is so common in Williams syndrome, some have argued that it should be part of the defining characteristic (Annaz et al. 2011; Shelton and Malow 2021). Sleep problems in Williams syndrome have recently been added to the Williams syndrome clinical management guidelines (William Syndrome Guidelines Development Group, 2017).

Köse et al (2017) also showed a 3-fold increase in the level of sleep disturbance in 142 children between the ages of 2 – 18 years of age diagnosed with autism spectrum disorder (ASD) compared to children of the same age without the condition. There was also a 3-fold increase in the level of sleep disturbance in the parents of children with ASD.

Prevalence: The prevalence of pediatric insomnia in children that goes beyond bedtime refusal and night awakenings ranges from 1% to 6% in the pediatric general population and is as high as 50% to 75% in children with neurodevelopmental or psychiatric comorbidities (Mindell et al, 2006).

The prevalence of sleep disorders in neurogenetic disorders is high and reported to be between 20-80%. For example, the prevalence in Angelman Syndrome is reported to be between 20-80% (Williams et al. 1995; Williams et al. 2006; Shelton and Malow, 2021). Over 80% of individuals with Rett syndrome are affected by sleep disorders, which vary with age and mutation type (Young et al. 2007; Tascini et al. 2022). Sleep problems are common in Tuberous Sclerosis Complex (TSC) patients (Bruni et al. 1995) and a high rate of sleep disturbances is reported in William's syndrome, as early as 18 months old (Gwilliam et al. 2020; Shelton and Malow 2021).

Demographics of the Population in the Authorized Indication: The population is composed of children with ASD (including autistic disorder, Asperger's disorder, and pervasive developmental disorder) and NGD (such as: Smith Magenis Syndrome [SMS], Angelman syndrome [AS], Rett syndrome, Tuberous sclerosis complex [TSC] and Williams syndrome)) (Phillips and Appleton, 2004; Krakowiak et al, 2008; Miano and Ferri, 2010; De Leersnyder et al, 2011; Jan and Freeman, 2004; DSM-5, 2013; Shelton and Malow 2021; Bruni et al. 1995).

Risk Factors: Recent studies suggest that the prevalence of sleep disorders in children with developmental disabilities ranges from 25% to 86%, and that these sleep disorders are frequently chronic, characterized by difficulties initiating or staying asleep, reported by caregiver, and usually far more difficult to treat than their normally developing peers (Cohen et al, 2014).

Main Existing Treatment Options: Current practices recommend parent-directed behavioral sleep interventions as first-line treatment for pediatric insomnia in ASD/NGD with reportedly

25% response rate (Malow et al, 2012; Gringras et al, 2012). Pharmacotherapy is often provided when behavioral intervention fails. Slenyto was initially approved by the EMA in 2018 for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. Subsequently, in August 2024, the indication was extended for other neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient.

In addition to Slenyto, there are a number of nationally authorised products in EU/EEA (benzodiazepines, benzodiazepine receptor agonists, antipsychotics and antihistamines) for the treatment of short-term or transient insomnia which could be used in this population, however none of these products are approved to treat insomnia in children based on the pathophysiological mechanism that is the cause of insomnia in these populations.

Moreover, the products which are currently authorised to treat insomnia are only authorised to treat short-term or transient insomnia, are not addressing sleep maintenance problems and do not share a similar favorable safety profile to Slenyto. As these drugs have not been specifically developed for the pediatric population, they lack an age-appropriate pharmaceutical form which is critical for compliance and acceptance in this target population. These products have not been tested in well controlled studies in the pediatric population.

Results of three surveys and a retrospective chart review showed that pediatricians and psychiatrists are prescribing nine classes of drugs to children for sleep disturbances (Hollway and Aman, 2011).

The most commonly prescribed medications are antihistamines, alpha-adrenergic agonists, antidepressants, over-the-counter melatonin, antipsychotics, benzodiazepines, and ‘‘Z-drugs’’ (zaleplon and zolpidem). Most of these medications are being used for their sedative adverse effects rather than for primary effects on sleep/wake mechanisms or hyper-arousal.

Despite the widespread use of these prescription therapies and other products, including antihistamines, little data exists on their efficacy for the treatment of insomnia in children and adolescents. Moreover, polysomnographic recording of some of the above hypnotic agents elicit changes in sleep architecture and reduced Rapid Eye Movement (REM) sleep and Slow Wave Sleep (SWS) (Barbanoj et al, 2005; Seibt et al, 2008).

These results may have important implications on the sleep disturbances treatment in children who are intellectually disabled, as both REM sleep and SWS play a role in the consolidation of procedural memory and the enhancement of synaptic plasticity (Hollway and Aman, 2011).

The mechanism of action of prolonged release melatonin on sleep latency, sleep maintenance and total sleep time is independent of the background disorder. Thus, children and adolescents with ASD and/or neurogenetic disorders and sleep disturbances associated with aberrant diurnal melatonin secretion and/or nocturnal awakenings will benefit from prolonged release melatonin. The benefit-risk balance of Slenyto for this patient population is considered

favourable in comparison to all other on label or off-label used insomnia medications commonly used in children.

Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity: Accumulating literature data continue to support the notion that children and adolescents who suffer from discontinuous sleep with frequent awakenings throughout the night, have increased tendency of hyperactivity, irritability, restlessness, poor concentration, impulsiveness, suicide risk, and poor memory.

In children with neurodevelopmental disorders, these sleep disorders may result in additional learning and behavior problems. Families of children with sleep disturbances also suffer, exhibiting negative effects on daytime function and well-being, as well as elevated levels of family stress.

Children with disturbed and discontinuous sleep with frequent awakenings throughout the night will usually disturb their parents' and siblings' sleep. This results in secondary detrimental physical, emotional, and social effects on the family, which when chronic, can even affect their ability to continue in employment or further education. Finally, chronic sleep disturbance in disabled children is a frequent cause of families placing their children into care (Doo and Wing, 2006; Appleton and Gringras, 2013; Appleton et al, 2012).

Important Co-morbidities: There are many conditions comorbid to ASD and NGD, including:

- Anxiety
- ADHD
- Developmental coordination disorder
- Epilepsy
- Fragile X syndrome
- Intellectual disability
- Obsessive compulsive disorder
- Sensory problems

Other conditions with a possible association with autistic spectrum disorders include:

- Bipolar disorder
- Bowel disease
- Gender dysphoria
- Neuroinflammation and immune disorders
- Psychopathological disorders such as phobias and depression

- Tourette syndrome

This population is highly medicated for numerous concomitant comorbidities. Therefore, it is likely that they may be receiving medications such as anti-epileptics, antidepressants (selective serotonin reuptake inhibitor), stimulants, mood-changing drugs and beta-blockers or antipsychotics.

Proposed additional indication: Slenyto is indicated for the treatment of insomnia in children and adolescents aged 6 – 17 years with Attention Deficit Hyperactivity Disorder (ADHD), where sleep hygiene measures have been insufficient.

Incidence:

Rates of ADHD diagnosis vary across countries and also temporally and geographically within countries. In Catalonia Spain, the overall annual incidence of ADHD diagnoses in 2009–2017 was assessed for all children aged 4 to 17 years based on the ICD-9 code 314 (hyperkinetic syndrome of childhood) (Pérez-Crespo et al, 2020). In this study a statistically significant increase in the incidence of ADHD diagnoses did not occur during the reporting period. The incidence of new ADHD cases followed an oscillating nonlinear pattern from 0.51% (95% CI 0.50, 0.52) in 2009 to 0.58% (95% CI 0.57, 0.59) in 2017. After stratifying by sex, the incidence of ADHD diagnoses was higher in boys compared to girls over all the study period, although a statistically significant increase of incidence of ADHD diagnoses for any sex was not observed. Regarding the age groups at the time of diagnosis, a higher number of new diagnoses of ADHD in children aged 7 to 12 years over all the study period was observed, mainly between the years 2009 and 2013, although no statistically significant differences in the temporal trends of incidence was identified when the data was stratified by age groups. The mean age of ADHD diagnosis was estimated to be 10.4 years, and the median age was 10 years. The greater diagnosis of new cases of ADHD over all the study period among children aged 7 to 12 years may be explained by the fact that this age group corresponds to the elementary school period where ADHD symptoms tend to be noticed and become more detectable.

In Norway, the incidence of ADHD was assessed based on a registered diagnosis of ICD-10 Hyperkinetic Disorder and ADHD medication use in a Danish register-based cohort of children born between 1990 and 2000 (Madsen et al. 2015). In this study, the incidence steadily increased with each birth year from 0.36 % (95 % CI 0.31; 0.41) in the 1990 birth cohort to 2.58 % (95 % CI 2.46; 2.70) in the 2000 birth cohort, with a mean incidence overall of 1.19 %.

Seventy percent of children with ADHD experience sleep problems (Becker et al., 2018; Sung et al., 2008) as opposed to only twenty to thirty percent in healthy children (Quach, 2012).

Sleep disturbance in children with ADHD

Children with ADHD have been found to have a delayed endogenous circadian pacemaker as measured by delayed sleep onset, dim light melatonin onset, and time of awakening (Van der Heijden, 2007, Smits 2001, Smits 2003, Van der Heijden, 2005).

Sleep problems are heterogenous in nature in children with ADHD and include all insomnia disorder symptoms as described in DSM-5: Higher bedtime resistance, sleep onset difficulties (Cortese et al., 2009), lighter sleep (Diaz-Roman, 2016), poor sleep quality, fragmented sleep with periods of nightly awakenings due to restlessness or movements (Bondopadhyay, 2021), and shorter sleep duration (Bondopadhyay, 2021; Becker, 2020).

Children with ADHD have been shown to experience 30 to 60 minutes shorter sleep duration and have significantly more awakenings at night when they are compared to healthy children (Cortese et al., 2009; Eyuboglu, 2018; Lycett et al., 2015; Tong, 2018).

These sleep disorders can also result in daytime sleepiness which negatively affects the children's quality of life (Langberg et al., 2020) and accentuates the observed negative behaviours seen in ADHD children (Bondopadhyay, 2021; Eyuboglu, 2018; Craig et al., 2020; Yoon, 2012).

Prevalence:

Significant variability in ADHD prevalence estimates worldwide have been reported, largely explained by the methodological procedures used. The updated European Consensus Statement, advise that childhood ADHD is among the most common psychiatric disorders with a prevalence rate of 3–5 % (Kooij et al 2019).

A meta-analysis of 19 studies with over 55,000 participants found that 5.9 % of children and adolescents meet diagnostic criteria for ADHD (Willcutt, 2012). Another meta-analysis, with 135 studies and about a quarter of a million children and adolescents, found no significant differences in prevalence between North America and Europe, Asia, Africa, South America, and Oceania (Polanczyk et al., 2014). The latter meta-analysis found no increase in the prevalence of ADHD in children and adolescents over the past three decades (Polanczyk et al., 2014). Although the prevalence of ADHD has not changed in this time period, large studies from the U.S. and Sweden indicate that ADHD is more likely to have been diagnosed in recent years, which reflects changes in administrative and clinical practices (Faraone et al., 2021).

Seventy percent of children with ADHD experience sleep problems (Becker et al., 2018; Sung et al., 2008) as opposed to only twenty to thirty percent in healthy children (Quach, 2012).

Demographics of the Population in the Proposed Indication:

The proposed indication is for the treatment of insomnia in children and adolescents aged 6 – 17 years with ADHD, where sleep hygiene measures have been insufficient.

A systematic review was done examining the studies reporting the age of onset/diagnosis of ADHD in European countries (28 European Member States plus 2 European Economic Area countries), published between January 1, 2010 and December 31, 2019 (Rocco et al 2021). The age range in the 24 studies reporting the mean age of diagnosis of ADHD was 6.2 to 18.1 years. However, the lowest mean age of onset in the children diagnosed with ADHD was 2.25 years. There is a large distance between the age of onset and the age of diagnosis. Early identification

of ADHD may facilitate early referral and treatment and this is crucial for greater success in reducing both the core symptoms of ADHD and its medium- and long-term effects.

ADHD is more common in males. A meta-analysis of parent ratings of symptoms in 29 studies with over 42,000 participants, and teacher ratings in 24 studies with over 56,000 participants, found a roughly two-to-one male/female ratio in children and adolescents (Willcutt, 2012).

People diagnosed with ADHD have an elevated risk for school failure, antisocial behavior, other psychiatric problems, somatic disorders, drug and alcohol abuse, accidental injuries, and premature death, including attempted and completed suicide. As a result, ADHD carries a significant financial burden to society. Several medications are effective for treating ADHD and for preventing many adverse outcomes (Faraone et al 2021). However, it is noted that the stimulant medications used as first line ADHD treatment, all have the potential to further increase sleep latency (time to fall asleep), thus compounding innately poor sleep quantity and quality (Thapar, 2016; Dalrymple et al., 2020; Faraone et al., 2019) and exacerbating the negative behaviors associated with ADHD.

The main existing treatment options:

A number of melatonin immediate release (IR) formulations are approved in the EU/EEA to treat insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. These products have been approved based on well-established use (WEU; Article 10a of Directive 2001/83/EC) demonstrating that melatonin has been used extensively in the EU/EEA in this indication for at least 10 years with recognised efficacy and an acceptable level of safety. Additionally, there are a number of nationally authorized products in EU/EEA (benzodiazepines, benzodiazepine receptor agonists, antipsychotics and antihistamines) for the treatment of short-term or transient insomnia which could be used in this population as no age population is referenced in the authorized insomnia indication and no pediatric contraindication is listed, however none of these products are approved to treat insomnia in children based on the pathophysiological mechanism that is the cause of insomnia in these populations.

Natural history of the indicated condition in the population, including mortality and morbidity:

Insomnia in children has a substantial negative impact on the day-to-day functioning, behaviours and cognitive performance of the child and can lead to distress for the entire family, including serious implications on parental employment and marital life. If left untreated, especially in children under 6 years of age, insomnia has the potential to exacerbate the core symptoms of ADHD (Rocco, 2021).

Children with neurodevelopmental disorders including ADHD are especially susceptible to the deleterious effects of sleep impairments in early ages as they tend to develop insomnia and other sleep disorders at early ages (as early as 6 months) (Scott et al., 2013). ADHD youth

show a maturational delay and potential topographical disruption in slow wave activity (SWA) during childhood and steeper decline throughout adolescence, suggesting faster synaptic pruning (Ricci et al, 2022).

Emerging early in childhood development, insomnia has impact on the child across a range of home, school and community contexts. Treating insomnia early might ameliorate the sleep-related deficits in brain development and would result in better outcomes in core symptoms improvements (Chawner et al., 2023).

Important co-morbidities:

Many large epidemiologic and clinical studies show that ADHD often co-occurs with other psychiatric disorders, especially depression, bipolar disorder, autism spectrum disorders, anxiety disorders, oppositional defiant disorder, conduct disorder, eating disorders, and substance use disorders (Faraone et al. 2021).

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table 2 Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
Toxicity: 1) Thyroid neoplastic tumors	The incidence of thyroid neoplastic tumors observed in the 104-week rat carcinogenicity study showed a total incidence of neoplastic thyroid changes (B-C cell adenomas + M-C cell carcinomas + B-follicular cell adenomas + M-follicular cell carcinomas + M-carcinoma) which was higher in male rats at all melatonin dose levels compared to controls; this difference was not significant (Covance Study Number 1829/001, Final Report, Volume 1, Table 13-9, page 346). The mean incidence of non-neoplastic B-follicular cell hypertrophy was higher in males of the intermediate (75 mg/kg/day) and high (150 mg/kg/day) dosage groups than in the controls; this difference was not significant. The incidence of non-neoplastic follicular cell hyperplasia and diffuse and focal C-cell hyperplasia were comparable in the control group compared to all doses, both in males and females (Covance Study Number 1829/001, Final Report, Module 4.2.3.2, Volume 1, Table 13.6, page 332). Increases in thyroid follicular cell hypertrophy are common responses in rats exposed to a number of xenobiotics particularly those which induce hepatic microsomal enzymes, e.g. phenobarbital (McClain, 1989). It is apparent from the 13-week and 26-week toxicity data that the changes observed in the livers of male rats exposed to high doses of melatonin (75 or 150 mg/kg/day) were consistent with hepatic microsomal enzyme induction. It appears highly probable based on available data that a significant increase in glutathione S-transferase activity and glucuronyl transferase activity in normal rats exposed to melatonin would have accelerated the metabolism of thyroxine and stimulated thyroid stimulating hormone (TSH) release. Hepatic microsomal enzyme induction is known to change the metabolism of hormones including thyroxine by accelerating the metabolic elimination of thyroxine. This decline in thyroxine may have been compensated for by release of increased levels of TSH from the anterior pituitary. Increased TSH levels can produce a variety of changes in the thyroid follicular cell including induction of hyperplasia and hypertrophy. The special susceptibility of the rat to thyroid neoplasms produced in this way has been considered by academic and regulatory agencies (International Agency for Research on Cancer [1974] and US Environmental Protection Agency [1986]) and is widely accepted as not indicating a risk in humans. Analysis of available blood samples (Study Number 1829/007) and from the 13-week toxicity study in rats (Study Number 1829/001) for plasma levels of TSH, T3 and T4 has been completed and the data were presented to the EMEA (FUM 002). Increased TSH levels were observed with the higher dose at 13 weeks, strengthening the evidence that multiple organ adaptation occurs when the liver and pituitary-thyroid axes are involved. These results would be expected if liver enzyme induction was the origin of the thyroid tumors and support the hypothesis above. In humans, microsomal enzyme inducers do not alter thyroid hormone levels until induction sufficient to increase antipyrine clearance by approximately 60% is achieved. Since human epidemiological studies have shown little, if any, increased risk of thyroid cancer in areas of

	widespread endemic goiter in which marked alterations in thyroid function occur, it is unlikely that there is any increased risk in man from discontinuous exposure to low levels of melatonin. A double-blind, parallel group, randomized, placebo-controlled study investigated the effect of add-on melatonin (Circadin 2 mg, prolonged release melatonin) or placebo in patients with nocturnal hypertension who were being treated with angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, beta-adrenoceptor blockers, or diuretics during the previous two months (Study Number NEU:BP). Circadin 2 mg or placebo was administered to 38 patients for four weeks. Absolute T3, free T4 and TSH data collected during the study indicated that there was minor, statistically, and clinically insignificant fluctuations between baseline and treatment periods at therapeutic doses, and that the recorded hormone levels did not differ between the treatment and placebo groups. Thus, the data from this clinical study on TSH, T3 and T4 does not suggest any effect of Circadin on the levels of these hormones. These data provide reassurance that the effects observed in the rat are not of clinical significance. Considering follicular hypertrophy is common in rats and the lack of thyroid tumors in the carcinogenicity studies, it is considered that the human risk of thyroid follicular cell hyperplasia and neoplasia with Circadin is minimal. Indeed, the Rapporteur has concluded that "Since in Section 5.3 of the Reference Safety Information (RSI) it is stated that the mechanism of thyroid tumors is under investigation, the text deserved an update in line to the conclusions presented herewith. The update may be a reformulation of the text by referring that the carcinogenicity study in the rat did not reveal any effect which may be relevant for humans". Following this conclusion, the RSI of Circadin was amended under a Type II variation to include the following text: “The carcinogenicity study in the rat did not reveal any effect which may be relevant for humans.”. Although the human risk of thyroid follicular cell hyperplasia and neoplasia with melatonin (Slenyto) no longer represent an area of risk, the Company will continue to carefully examine any relevant post-marketing safety reports but needs no further proactive assessment.
Toxicity: 2) Sexual maturation and development	There is an absence of any sustained effects of melatonin in the repeat-dose, reproduction and juvenile non-clinical applicant-sponsored toxicology studies on sexual maturation and development. Nevertheless, this safety concern is discussed below because of the role of melatonin in the reproductive system as described in various publications. Melatonin regulates the reproductive process in seasonal but not in continuous breeders: however, it delays sexual development in the rat in a transient and reversible manner (Lang, 1986; Lang et al, 1984). Melatonin is a signal of darkness in the organism and its administration during daytime creates a state of night, or of winter season in the animal. Melatonin responsiveness can only be demonstrated when melatonin is given outside the time that it is present endogenously - namely during daytime. The response is characterized by windows of sensitivity (juvenile stage) and transient nature to allow proper adjustment of the organism to the changing environmental light/dark and seasonal cycles. All of these effects are reversible, and none lead to organ toxicity. The reproductive system of rats is sensitive to melatonin only during the period of 20 to 40 postnatal days. Administration of melatonin during this period delays the pubertal development of the rat. However, if melatonin is given to young rats after postnatal day 40 there is no effect whatsoever

	of the hormone on their pubertal development and reproductive functioning (Lang, 1986; Lang et al, 1984). Furthermore, even if melatonin is given in the window of 20 to 40 postnatal days and thereafter, its effect dissipates within several days and the overall result is a delay in pubertal development, but no effect on reproductive function despite continuous treatment with melatonin. Of note, the delay of pubertal development by melatonin in the rat is only observed if melatonin is given in either one of two time windows, in the morning and in the afternoon (because these are the times that represent the natural variability in day length to which the animals physiological system is responding) and is not seen when melatonin is given at night to the animals, a period that is characterized by elevated endogenous production of the hormone at all times (Lang, 1986). The administration of melatonin in the repeat-dose, reproduction and juvenile non-clinical toxicology studies was performed in the morning in the repeat-dose and juvenile toxicity studies, and in the afternoon for the reproduction toxicity studies, so as to be able to detect sustained effects of the hormone if there are any. The applicant has conducted a repeated dose toxicity and toxicokinetic study in rats from weaning to sexual maturation under the agreed Pediatric Investigational Plan. The purpose of this study (G7714, Module 4.2.3.5.4) was to assess the systemic toxicological and toxicokinetic profile of the test item, melatonin in juvenile Sprague Dawley rats when administered orally by gavage for a period of 70 days, and also to assess the reversibility of any effects following a 14-day recovery period. Clinical pathology investigations revealed treatment-related reversible increase in reticulocyte count and total bilirubin in females at 160 mg/kg/day. The reversible increase in liver weights was observed in males at the ≥ 80 mg/kg/day dose and in females at the 160 mg/kg/day dose, and that in spleen weights in females at the 160 mg/kg/day dose. The organs with microscopic findings in females included a non-reversible minimal increase in extramedullary hematopoiesis at 160 mg/kg/day dose in the spleen. Treatment with melatonin at dose levels of 20, 80 and 160 mg/kg/day to Sprague Dawley rats had no effects on general health, body weights, net body weight gains, food consumption, estrous cycle, sexual maturation, and sperm parameters. The evaluated “No Observed Adverse Effect Level” is 80 mg/kg/day. It is to be noted that in wildlife, even animals that are seasonal become refractory to the endocrine effects of exogenous melatonin given in either the morning or evening, within 6 to 8 weeks as they must prepare themselves for the next season. Thus, the absence of any sustained effects of melatonin in the repeat-dose, reproduction and juvenile non-clinical toxicology studies is in full agreement with the temporary and transient nature of these effects of melatonin in all animals including rats. Moreover, in clinical study NEUCH7911, the applicant assessed the treatment effect of Slenyto 2, 5, and 10 mg on children’s pubertal status using the Tanner scale in children ≥ 8 years of age. For children ≤ 5 years of age, height and head circumference were used to stage children’s development. Between the age of 5 and 8 the children’s physical development was determined using the BMI (baseline through Week 108). Currently the applicant submitted data for up to 24 months. Change from baseline for standard deviation scores of pubic hair, breast and genitalia development are presented in the Study CSR Module 5. After 3 months of double-blind treatment there were no apparent differences

	between Slenyto and placebo for Tanner assessments of pubertal development. No differences were noted between the groups after the additional 3-month open-label period when both groups were on active treatment. Moreover, the Tanner scale was assessed at Visit 8 after 104 weeks of treatment (104 weeks of treatment with Slenyto for the active randomized group and 91 weeks of Slenyto treatment for the placebo randomized group). The results of this assessment showed that there was no delay in sexual maturation after 2 years of active treatment, as the mean SD values were well within the normal percentile and when looking at the range of values, there was no child who was delayed in sexual maturation. In addition, the mean BMI Z score after 2 years in the study population was around 1.1 for the total group and the range was -2.39 – 3.55 which is considered normal distribution. In addition, post marketing data from the reference product, Circadin, that has been marketed since 2007, is monitored routinely and does not indicate any potential signal towards effects on maturation in this population. Circadin is used off label extensively in this population and under a Temporary Registration Use (RTU) in France. The program was held from 2015-2021 and included a total of 1,100 patients that were enrolled in this study. Of those patients, 1,038 were treated with Circadin, 926 were eligible, including 839 with ASD, 35 with SMS, 29 with Angelman syndrome, 15 with Rett syndrome, and 8 with Tuberous sclerosis complex. The mean daily dose in the RTU was 3.3 mg/day. The report included demographic data including age, gender, height, and weight (at each visit), adverse events, compliance, efficacy, concomitant medications for insomnia, and reasons for discontinuation. RTU follow-up of patients' height, weight, and BMI over periods P1(0-7 months) to P9 (49-55 months) showed that medians of z-scores (height, weight, and BMI) for almost all patients were between -2 and +2 standard deviations (SD) which is considered within the normal range. Hence, melatonin delays sexual development in the rat in a transient and reversible manner, which corroborates the absence of any sustained effects of melatonin in the repeat-dose, reproduction, and juvenile non-clinical toxicology applicant-sponsored studies. No effects were measured in the clinical study following up to 24 months treatment and under the RTU up to 55 months of treatment. Thus, the initially determined important potential risk of “delay of sexual maturation and development” was removed by EMA following their review of the sixth and final annual RTU report (covering the period of 01 October 2015 to 01 October 2021) under Post-Authorisation Measure REC002.2. However, the MAH continues to closely monitor the safety concern "Delay of sexual maturation and development” through routine pharmacovigilance in the PSURs, including an in-depth analysis of any new data related to this risk and long-term use.
Toxicity: Use in pregnancy and lactation	Transfer via breast milk and/or physiological excretion of melatonin into maternal milk have been shown in different animal species and humans; additionally melatonin crosses the placenta and shows rhythmic variations in breast milk, in parallel with plasma, in both humans and goats. Circadian variation of serum melatonin levels has been observed in pregnant and lactating female Wistar rats. These data suggest that circadian variations in circulating serum melatonin levels in fetal and suckling rats are dependent on maternal melatonin transfer. Timed administration of melatonin during pregnancy in rodents is reported to set the phase of circadian rhythms in the pups (Arendt, 1997). Transfer

	of melatonin via breast milk has also been demonstrated in rodents, sheep primates and bovine species. Arendt concludes that administration of melatonin to pregnant women is, therefore, likely to result in fetal exposure to excess melatonin and could modify subsequent development in terms of the circadian system and the timing of puberty. However, it should be noted that the author's comments relate to fast release, low dose melatonin (0.05 to 10 mg) and she indicates that some of the potential adverse effects of melatonin including long-term reproductive effects may be avoided by intermittent use. It is important to note that in the applicant-sponsored Oral (Gavage) Study of Pre- and Postnatal Development in the Rat (1476/005, Module 4.2.3.5.3), administration of melatonin at dose levels of 0 (control), 15, 55 and 200 mg/kg/day to groups of 24 pre-mated parental females from Day 6 of gestation to Day 21 post-partum (inclusive) had no effects on the subsequent wellbeing of the F1 generation at these doses. No effects on clinical observations, body weight and food intake were observed. Physical development, as assessed by the time of balano-preputial separation and vaginal opening, and functional development as assessed by in-cage activity and learning (swimming maze), showed no dose-related effects. The mating performance, fertility, and outcome of pregnancy of the F1 animals showed no dose-related effects. Company-sponsored studies Oral (Gavage) Study of Embryo-Fetal Development in the Rabbit (1476/004, Module 4.2.3.5.2) and Oral (Gavage) study on fertility and early embryonic development in the rat (1476/006, Module 4.2.3.5.1) have revealed no effect on fertility, embryonic and fetal development in rat and rabbit. Melatonin is present endogenously in human milk. Melatonin measured in breast milk collected over a 24-hour period within 3 months of delivery exhibited a pronounced daily rhythm, with high levels during the night and undetectable levels during the day. It has been proposed that the presence of this rhythm in breast milk might communicate time of day information to breastfed infants. The RSI includes a discussion on the use of Slenyto during pregnancy or lactation. However, as there is potential for off-label use, any reported pregnancies will be monitored appropriately through routine pharmacovigilance practices. Use in pregnancy and lactation is specified under summary of safety concerns as missing information in the current RMP.
General safety pharmacology: Cardiovascular (including potential for QT interval prolongation), central nervous system.	In the literature there was one report in albino rats, where melatonin administration (0.1 mg, intraperitoneal) resulted in increased light-induced damage to the retinal outer nuclear layer. On the other hand, there is evidence in the literature that melatonin may have a protective role in the nitric oxide elevated retina in rats. Melatonin also protects retinal pigment epithelial cells against oxidative stress. There was no evidence for retinal toxicity in the company-sponsored combined toxicity/oncogenicity study in the rat (Neurim 1829/001, Module 4.2.3.2). Histopathological examinations of the eyes were performed during weeks 13, 26 (and during the treatment-free period), and 104. The results indicate no microscopic pathology associated with the eyes at any of these time points. A single case of a reversible visual acuity loss, dyschromatopsia, and altered light adaptation was reported in the prototype melatonin monograph prepared by the Committee on the Framework for Evaluating the Safety of Dietary Supplements of the National Academies at the request of the United States Food and Drug Administration. A 42-year-old woman had

	taken Zoloft for 4 years and began a high protein diet with melatonin supplementation 2 weeks before onset of visual symptoms. Neuro-ophthalmologic examination was otherwise normal except for evolving bilateral cecocentral scotomas. Visual acuity and color vision improved within 2 months after melatonin and the high protein diet were discontinued. A high protein diet may increase levels of tryptophan which is a precursor of melatonin. This in combination with Zoloft, a serotonin re-uptake inhibitor, might increase melatonin production. It is not clear if the reversible ocular symptoms were related to melatonin or the high protein diet, their combination, or combination with Zoloft, or was just incidental. Neurim-pooled clinical safety data containing nearly 2000 patients on the reference product Circadin does not contain any cases of retinal toxicity or visual acuity loss, dyschromatopsia, or altered light adaptation. This represents an area of low potential for risk based on experience so far, but post-marketing adverse event reports involving any form of visual disturbance will be closely monitored and any findings addressed specifically within Periodic Safety Update Reports.
Mechanisms for drug interactions	There are no issues to report that are not already covered in other parts of the RMP.
Other toxicity-related information or data	There are no other non-clinical, toxicity-related safety issues to address.

Abbreviations: BMI = body mass index; CSR = clinical study report; RMP = risk management plan; RSI = reference safety information; RTU = Temporary Registration Use; TSH = thyroxine stimulating hormone.
Data source: On file.

Important potential risks (not refuted by clinical data or which are of unknown significance)

- Thyroid follicular cell hyperplasia and neoplasia

Considering follicular hypertrophy is common in rats, the lack of thyroid tumors in the carcinogenicity studies, and lack of effect of Circadin on TSH, T3 and T4 levels in a clinical study, it is considered that the human risk of thyroid follicular cell hyperplasia and neoplasia with Slenyto is minimal.

Although the human risk of thyroid follicular cell hyperplasia and neoplasia with Slenyto no longer represent an area of risk, the Company will continue to examine any relevant post-marketing safety reports carefully, but no further proactive assessment is required.

- Transfer via breast milk and/or physiological excretion of melatonin into maternal milk

The results of the reproduction toxicity studies show lack of any effects on the fetus and F1 generation. Slenyto is proposed only for use in patients of 2 to 18 years of age. The transfer via breast milk is thus of little relevance to this age group. However, the summary of product characteristics (SmPC) of Slenyto includes a discussion on the use of Slenyto during pregnancy and breastfeeding under section 4.6.

- Sexual maturation and development

Melatonin delays sexual development in the rat in a transient and reversible manner, which corroborates the absence of any sustained effects of melatonin in the repeat-dose, reproduction and juvenile nonclinical toxicology applicant sponsored studies. No effects on sexual maturation and growth were measured in the Slenyto clinical study following up to 24 months' treatment at 2, 5 and 10 mg/day, or under the French RTU following up to 55 months of treatment with the reference product Circadin at 2-6 mg/day.

The sixth and final annual RTU report (covering the period of 01 October 2015 to 01 October 2021) was completed in March 2022 and submitted to the EMA for assessment under Post-Authorisation Measure REC002.2. As there was no evidence of a delay in sexual maturation and development, the EMA agreed to its removal from the RMP as an important potential risk. However, the MAH continues to closely monitor the safety concern "Delay of sexual maturation and development" through routine pharmacovigilance in the next PSURs, including an in-depth analysis of any new data related to this risk and long-term use.

- Potential for Retinal Effects

There was no evidence for retinal toxicity in the company-sponsored combined toxicity/oncogenicity study in the rat (Neurim1829/001). In the literature there was one report in albino rats, where melatonin administration (0.1 mg, intraperitoneal) resulted in increased light-induced damage to the retinal outer nuclear layer. This represents an area of low potential for risk based on experience so far, but post-marketing adverse event reports involving any form of visual disturbance will be monitored through routine pharmacovigilance practices.

MODULE SIII CLINICAL TRIAL EXPOSURE

At present, the reference product Circadin (prolonged release melatonin) 2 mg is authorized for use in one indication (primary insomnia) and one patient population (patients aged ≥55 years). An increase in the maximum recommended duration of use from 3 weeks to 13 weeks was approved by the European Medicines Agency on 22 Apr 2010.

The clinical trial exposure used to support the initial Marketing Authorisation for Slenyto for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient is presented in Tables 3 to 6.

Clinical Trial Exposure by Duration of Exposure

Table 3 Extent of Exposure by Duration (by Indication)

Insomnia in children and adolescents aged 2 to 18 years with ASD		
Duration of exposure	**Persons**	**Person time (patient weeks)**
Acute (Pharmacokinetic Study)	16	4
13 weeks (double-blind period)	51	663
13 weeks (open-label period 1)	95	1235
13 weeks (open-label period 2)	85	1105
13 weeks (open-label period 3)	79	1027
52 weeks (open-label period 4)	74	3,848

Table 4 Extent of Exposure by Duration (Totals)

Duration of exposure	**Persons**	**Person time (patient weeks)**
Insomnia in children and adolescents aged 2 to 18 years with ASD (accumulative, 13 weeks)		
Total person time	384	7,878

Clinical Trial Exposure by Dose

Table 5 Extent of Exposure by Dose (Totals)

Insomnia in children and adolescents aged 2 to 18 years with ASD		
Dose of exposure	**Persons**	**Person time (patient weeks)**
2 mg (one administration, Pharmacokinetic Study)	16	2
10 mg (one administration, Pharmacokinetic Study)	16	2
2 mg (13 weeks, double-blind period)	23	299
2 mg (13 weeks, open-label period 1)	18	234
2 mg (13 weeks, open-label period 2)	15	195
2 mg (13 weeks, open-label period 3)	15	195
2 mg (52 weeks, open-label period 4)	15	780
5 mg (13 weeks, double-blind period)	32	416
5 mg (13 weeks, open-label period 1)	40	520
5 mg (13 weeks, open-label period 2)	36	468
5 mg (13 weeks, open-label period 3)	32	416
5 mg (52 weeks, open-label period 4)	31	1,612
10 mg (13 weeks, open-label period 2)	34	442
10 mg (13 weeks, open-label period 3)	32	416
10 mg (52 weeks, open-label period 4)	28	1,456

Data source: Clinical study Report NEUCH7911, Table 14.3.1.4

Clinical Trial Exposure by Age Group and Gender

Table 6 Extent of Exposure by Age Group and Gender (Totals)

Insomnia in children and adolescents aged 2 to 18 years with ASD				
Age group	**Persons**		**Person time (patient weeks)**	
	Male	**Female**	**Male**	**Female**
0 to 18 (13 weeks double-blind)	38	13	494	169
0 to 18 (13 weeks open-label)	71	24	923	312
0 to 18 (13 weeks open-label)	63	22	819	286
0 to 18 (13 weeks open-label)	59	20	767	260
0 to 18 (52 weeks open-label)	54	20	2,808	1,040

Sexual Maturation and Development:

In clinical study NEUCH7911, the applicant assessed the treatment effect of Slenyto 2, 5, and 10 mg on children's pubertal status using the Tanner scale in children ≥ 8 years of age.

For children ≤ 5 years of age, height and head circumference were used to stage children's development. Between the age of 5 and 8 the children's physical development was determined using the BMI (baseline through Week 108).

Currently the applicant submitted data for up to 24 months.

Change from baseline for standard deviation scores of pubic hair, breast and genitalia development are presented in the Study CSR Module 5. After 3 months of double-blind treatment there were no apparent differences between Slenyto and placebo for Tanner assessments of pubertal development. No differences were noted between the groups after the additional 3-month open-label period when both groups were on active treatment.

Moreover, the Tanner scale was assessed at Visit 8 after 104 weeks of treatment (104 weeks of treatment with Slenyto for the active randomized group and 91 weeks of Slenyto treatment for the placebo randomized group). The results of this assessment showed that there was no delay in sexual maturation after 2 years of active treatment, as the mean SD values were well within the normal percentile (around 1.1) and when looking at the range of values (-0.43 - 3.04), there was no child who was delayed in sexual maturation. In addition, the mean BMI Z score after 2 years in the study population was around 1.1 for the total group and the range was -2.39 – 3.55 which is considered normal distribution.

In addition, post marketing data from the reference product, Circadin, that has been marketed since 2007, is monitored routinely and does not indicate any potential signal towards effects on maturation in this population. Circadin is used off label extensively in this population and under a Temporary Registration Use (RTU) in France. The program was held from 2015-2021 included a total of 1,100 patients that were enrolled in this study. Of those patients, 1,038 were treated with Circadin, 926 were eligible, including 839 with ASD, 35 with SMS, 29 with Angelman syndrome, 15 with Rett syndrome, and 8 with Tuberous sclerosis complex. The mean daily dose in the RTU was 3.3 mg/day. The report included demographic data including age, gender, height, and weight (at each visit), adverse events, compliance, efficacy, concomitant medications for insomnia, and reasons for discontinuation. RTU follow-up of patients' height, weight, and BMI over periods P1(0-7 months) to P9 (49-55 months) showed that medians of z-scores (height, weight, and BMI) for almost all patients were between -2 and +2 standard deviations (SD) which is considered within the normal range.

The sixth and final annual RTU report (covering the period of 01 October 2015 to 01 October 2021) was completed in March 2022 and submitted to the EMA for assessment under Post-Authorisation Measure REC002.2 (refer to SV.1.2 Exposure). As there was no evidence of a delay in sexual maturation and development, the EMA agreed to its removal from the RMP as an important potential risk. Thus, delay of sexual maturation and development is not considered a potential risk.

However, the MAH continues to closely monitor the safety concern "Delay of sexual maturation and development" through routine pharmacovigilance in the next PSURs, including an in-depth analysis of any new data related to this risk and long-term use.

No data are available by ethnic origin or in special populations (e.g., pregnant, or lactating women, patients with renal, hepatic, or cardiac impairment, immuno-compromised patients, sub-populations with genetic polymorphisms).

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 7 Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criterion	Reason for Exclusion	Considered as Missing Information (Y/N)	Rationale
Hypersensitivity to exogenous melatonin or lactose	Patients who have already had an allergic reaction due to melatonin or lactose are at a higher risk of experiencing a new reaction when melatonin or lactose is administered.	N	The SmPC has the following text: **Section 4.3** (Contraindications): Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (List of excipients). **Section 4.4** (Special warnings and precautions for use) Lactose: Slenyto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Age 0 to 2 years	Slenyto is only authorized for patients aged 2 to 18 years. There is no relevant use of Slenyto in children aged 0 to 2 years.	N	The SmPC has the following text: **Section 4.2** (Posology and method of administration, special populations) Pediatric population (under 2 years of age): There is no relevant use of melatonin in children aged 0 to 2 years for the treatment of insomnia.
Pregnancy and breastfeeding	Pregnancy and breastfeeding – in this population this would have minor effects due to the age range. Nevertheless, patients and parents are asked to consult the doctor if the patient is pregnant / breastfeeding or planning to do so.	Y	The SmPC has the following text: **Section 4.6** (Fertility, pregnancy, and lactation) Pregnancy: There is no data from the use of melatonin in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of melatonin during pregnancy. Breastfeeding: Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. Data in animals indicate maternal transfer of melatonin to the fetus via the placenta or in the milk. The effect of melatonin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from melatonin therapy taking into account

Exclusion Criterion	Reason for Exclusion	Considered as Missing Information (Y/N)	Rationale
			the benefit of breast feeding for the child and the benefit of therapy for the woman.
Renal or hepatic insufficiency	Slenyto is not recommended for use in these children as there is not enough experience in use in such conditions which are rare in this population.	N	The SmPC has the following text: **Section 4.2** (Posology and method of administration, special populations) Renal impairment: The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to patients with renal impairment. Hepatic impairment: There is no experience of the use of melatonin in patients with liver impairment. Therefore, melatonin is not recommended for use in patients with hepatic impairment (see section 5.2).
Treatment with any form of melatonin within 2 weeks prior to Visit 1	To avoid effects on the results of the study that should represent the pure effect of the investigational drug.	N	Previous consumption of melatonin in real life does not influence safety or efficacy of Slenyto treatment.
An untreated medical /ineffectively treated/psychological condition that may be the etiology of sleep disturbances	To focus in the study on the population indicated for treatment (children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.).	N	The proposed indication is “the treatment of insomnia.” Insomnia disorder is a DSM-5 diagnosis assigned to individuals who experience recurrent poor sleep quality or quantity that causes distress or impairment in important areas of functioning (APA DSM-5 Manual, 2013). According to DSM-5, to reach a diagnosis of insomnia disorder, the following criterion must be met: The difficulty cannot be better explained by other physical, mental, or sleep-wake disorders. Therefore, the differential definition of insomnia from other conditions that may affect sleep is an inherent part of the diagnosis made by the physician.
Unresponsive to previous Circadin therapy based on past medical history records in the last 2 years	Unresponsiveness in the past increase the chance that the sleep disturbance is not related to melatonin	N	There is no risk in treating such a population with melatonin.

Exclusion Criterion	Reason for Exclusion	Considered as Missing Information (Y/N)	Rationale
Known moderate to severe sleep apnea	To concentrate in the clinical study in the target population.	N	The differential definition of insomnia from other conditions that may affect sleep is an inherent part of the diagnosis made by the physician (see above).
Females of child-bearing potential who were not using contraceptives and/or were breastfeeding and who were sexually active (abstinence is an acceptable method of contraception)	To avoid treatment of pregnant women	Y	Pregnancy is part of the general warnings in the SmPC: **Section 4.6** (Fertility, pregnancy, and lactation) Pregnancy: There are no data from the use of melatonin in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of melatonin during pregnancy. Breastfeeding: Endogenous melatonin was measured in human breast milk thus exogenous melatonin is secreted into human milk. Data in animals indicate maternal transfer of melatonin to the fetus via the placenta or in the milk. The effect of melatonin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from melatonin therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.
Any other pharmaceutical hypnotic treatment, including benzodiazepines	There is a risk of a possible additive effect when melatonin is combined with another hypnotic drug. There is also a large amount of data in the literature regarding the effect of benzodiazepines and anti-depressants on endogenous melatonin secretion. The interaction with Zolpidem was studied as well and PD interaction was demonstrated with the reference drug	N	This exclusion criterion has been treated as a possible interaction in the SmPC: **Section 4.5** (Interaction with other medicinal products and other forms of interaction - Concomitant use not recommended) Benzodiazepines/Non-benzodiazepine hypnotics: Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention,

Exclusion Criterion	Reason for Exclusion	Considered as Missing Information (Y/N)	Rationale
	Circadin (Otmani et al, 2008).		memory and co-ordination compared to zolpidem alone. Combination with benzodiazepines and non-benzodiazepine hypnotics should be avoided.
Excessive consumption of alcohol	There is a large amount of data in the literature regarding the effect of alcohol on endogenous melatonin secretion. Whether or not alcohol interferes with the dynamic or kinetic effects of Slenyto or vice versa has not been studied. However, alcohol also reduces the effectiveness of Melatonin on sleep.	N	This exclusion criterion has been treated as a possible interaction in the SmPC: **Section 4.5** (Interaction with other medicinal products and other forms of interaction - Concomitant use not recommended) Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; ASD = Autism Spectrum Disorder; NGD = neurogenetic disorders; PD = pharmacodynamics; SmPC = summary of product characteristics.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare or very rare adverse reactions. Exposure data from two clinical trials in the targeted population is limited to 4030 patient weeks, cumulatively. The benefit-risk balance for the reference product, Circadin, has been well-established. However, the benefit-risk balance for Slenyto may alter as post-marketing experience in the pediatric population increases.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Children

The indication for Slenyto is in children aged 2 to 18 years, and this is the age group included in the clinical program under the approved Pediatric Investigational Plan. In addition, the reference product, Circadin, is used off-label extensively in this age group and also under a special Temporary Registration Use program in France.

The pediatric population from 0 to 2 years is not represented in our studies as non-pharmacological therapy would be preferred in this age group.

Elderly

The reference product, Circadin, is indicated for the monotherapy of primary insomnia in patients aged 55 years or older. Therefore, it would be expected that the clinical trial population has a much higher proportion of elderly patients than the general population. The justification for this particular age group is that endogenous melatonin production falls with increasing age such that insomnia is a common problem in more senior patients.

However, this age group of patients is also more likely to have other co-existing/underlying conditions and multiple concomitant medications. Therefore, the clinical trial population for Circadin will be over-representative of conditions associated with increasing age (arthritis, cardiovascular disorders, osteoporosis, etc.).

Table 8 below shows the numbers and age ranges of patients studied in all Neurim-sponsored clinical trials including trials conducted with the reference product Circadin (for ages 20 to ≥ 80 years).

Table 8 Number of Patients in Neurim-sponsored Trials

Grouping by Age (Years)	Male		Female	
	N	Weeks	N	Weeks
0 to 18 (13 weeks double-blind)	38	494	13	169
0 to 18 (13 weeks open-label)	71	923	24	213
0 to 18 (13 weeks open-label)	63	819	22	286
0 to 18 (13 weeks open-label)	59	767	20	260
0 to 18 (52 weeks open-label)	54	2,808	20	1,040
20 to < 30	9	309.86	7	253.86
30 to < 40	18	608.65	29	1060.12
40 to < 50	27	857.22	57	1878.83
50 to < 60	145	2441.70	296	5517.05
60 to < 70	243	2984	507	7393
70 to < 80	150	1844.74	281	3527.42
≥ 80	22	122.14	42	188.56

Data source: On file.

Pregnant or breastfeeding women

For melatonin, no clinical data are available following exposure during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy,

embryonal/fetal development, parturition, or postnatal development. In view of the lack of clinical data, use in pregnant women and by women intending to become pregnant should be considered only if necessary.

Endogenous melatonin has been measured in human breast milk and thus it is likely that exogenous melatonin is secreted into human milk. There is data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the fetus via the placenta or in the milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from melatonin therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

An appropriate statement and a discussion on the use of Slenyto during pregnancy and breastfeeding has been added to Section 4.6 of the Summary of Product Characteristics.

Patients with hepatic impairment

There are no company-sponsored clinical studies in place to examine the use of the reference product Circadin or Slenyto in patients with liver impairment.

The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels (Kopin et al, 1961). Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls (Steindl et al, 1995; Ardizzi et al, 1998).

Therefore, Slenyto is not recommended for use in patients with any classified hepatic impairment criteria (Child-Pugh classifications). This is reflected in the current labelling and there is a warning in Section 4.2 (Posology and method of administration) of the current SmPC stating that Slenyto is not recommended for use in patients with hepatic impairment.

Patients with renal impairment

Melatonin and its metabolites are excreted via the renal route. Company data indicates that there is no accumulation of melatonin after repeated dosing. This finding is compatible with the short half-life of melatonin in humans.

In an open-label study of the effect of the reference product Circadin 2 mg on melatonin levels, sleep, and safety parameters in patients with end stage renal disease on chronic hemodialysis, melatonin levels assessed in the blood of the patients at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411.4 ± 56.5 and 432.00 ± 83.2 pg/ml respectively, and are similar to those found in healthy volunteers following a single dose of

Circadin 2 mg. However, patients with mild, moderate, or severe renal failure were not studied in the clinical program.

There is a warning in Section 4.2 (Posology and method of administration) of the SmPC which states that, "The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to patients with renal impairment."

Patients with other relevant comorbidity

Patients receiving Slenyto may have neurological and psychiatric comorbidities; these patients were not excluded from clinical trials.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

This is not relevant to the conditions for which Slenyto is authorized (insomnia).

Sub-populations carrying known and relevant polymorphisms

There are no known and relevant polymorphisms concerning melatonin. Therefore, no specific testing has been performed to determine sub-populations carrying them.

Patients of different racial and/or ethnic origin

There is limited information available on patients from the reference product Circadin and Slenyto clinical trials of different racial or ethnic origins. Circadin has been studied in South Korea in a bridging study, with a similar efficacy and safety profile being demonstrated. Circadin has been approved in South Korea since 2014. Regarding Slenyto, as the development program was conducted in the United States and the European Union, the clinical trial population is mostly Caucasian but there were Hispanic or Latino (15.2%), Black or African American (7.2%) and Asian (1.6%) who demonstrated a similar safety and efficacy response.

MODULE SV POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

SV.1.1 Method Used to Calculate Exposure

There is no single daily dose for Slenyto; the dose is titrated from a starting dose of 2mg daily up to a recommended maximum of 10mg daily. However, the average daily dose is considered to be 5mg daily. Thus, taking the total number of milligrams of Slenyto that have been marketed and dividing it by 5 will produce an estimate of the total number of daily doses.

There is also no set treatment duration for Slenyto; treatment is continuous. Thus, taking the estimated number of daily doses and dividing by 365 will produce an estimate of the total number of patient-years of exposure.

SV.1.2 Exposure

CCI

Table 9 below provides an estimation of patient exposure in each country where Slenyto is currently authorized and available. The exposure calculations have been performed as outlined above.

Table 9 Number of tablets sold and estimated exposure (number of patient-years) since the first authorisation by country where Slenyto is authorised

Country	Number of daily 5mg doses	Estimated number of patient years	Percentage of total patient years
TOTAL	CCI	153,641	CCI
EEA			
EEA Total	CCI	123,011	CCI
CCI			

Country	Number of daily 5mg doses	Estimated number of patient years	Percentage of total patient years
CCI			
Rest of the world			
Rest of World total	CCI	30,631	CCI
CCI			

Post-authorization Use in Neurogenetic disorders - Smith-Magenis syndrome, Angelman syndrome (AS), Rett syndrome, Tuberous sclerosis complex (TSC)

In France, in July 2015, the National Agency for the Safety of Medicines (ANSM) issued a unanimous positive advice on the set up of temporary registration use (RTU) of Circadin in the treatment of sleep-awakening rhythm disorder in children above 6 years of age associated with:

- Rett syndrome
- Neurodegenerative diseases (Smith-Magenis syndrome, Angelman syndrome, Bourneville tuberous sclerosis [TSB])
- Autism spectrum disorders

The recommended posology of Circadin was 4 to 6 mg per day. Patients were followed-up according to protocol through an electronic web-page portal. The RTU was valid for an initial duration of three years which was subsequently renewed for a further three years.

In October 2015 the launch of the web-portal www.rtucircadin.fr and the eCRF were initiated; the first patient was included under the program in October 2015.

As of October 2021, 597 physicians had registered 926 patients in the program:

- 839 with autism spectrum disorders

- 35 with Smith-Magenis syndrome
- 29 with Angelman syndrome
- 15 with Rett syndrome
- 8 with TSB syndrome

The program protocol and the Annual Reports covering the six-year period from October 2015 to October 2021 have been submitted to EMA for assessment. The final Annual report no. 6, version dated 29 March 2022, with data collected from 01 October 2015 to 01 October 2021 was submitted to EMA as part of the post-authorization measure EMEA/H/C/004425/REC/002.2. The risk management plan (version 1.6) was subsequently updated with the outcome of this assessment and approved as part of the renewal (EMEA/H/C/004425/R/0021).

Post-authorization Use in the Elderly

Other than case reports received by Neurim and its partner companies of elderly patients receiving Slenyto (which are recorded on the global safety database), there are no quantitative records held by Neurim on use of Slenyto in this population. However, assuming that the proportion of case reports pertaining to elderly patients is a reasonable approximation of the proportion of elderly patients receiving Slenyto, then the proportion is 7.5% (CCI). The weaknesses of this assumption include the higher frequency of comorbidities in the elderly making the incidence of AEs (and therefore of reporting) more likely.

Post-authorization Use in Pregnant/Lactating Women

There is post-authorization information from Slenyto, which includes any case reports received by Neurim and its partner companies of Slenyto being used by pregnant or breastfeeding women (which are recorded on the global safety database). However, there are no quantitative records held by Neurim on use of marketed Slenyto in this population.

Since the first marketing of Slenyto, there have been no reports of pregnancy or breastfeeding women having received Slenyto.

Post-authorization Use in Hepatic and/or Renal Impairment

There is post-authorization information from Slenyto, which includes case reports received by Neurim and its partner companies involving patients with hepatic and/or renal impairment (which are recorded on the global safety database). However, there are no quantitative records held by Neurim on use of marketed Slenyto in this population.

As of the data lock point of this RMP, the total number of Slenyto cases in the database is CCI and out of these cases there were only two pediatric patients with hepatic impairment (jaundice and hepatic steatosis) and two pediatric patients with renal impairment.

Other Post-authorization Use

Sub-populations carrying relevant genetic polymorphism(s)

There are no genetic polymorphisms that are relevant to Slenyto. As the testing for such polymorphisms is complex and would only be indicated if a healthcare professional suspected that this was an issue with a patient, it is extremely unlikely that information on genetic polymorphisms would ever be provided by patients taking Slenyto.

Populations with specific racial and/or ethnic origins

There are no quantitative records held by Neurim on use of Slenyto in specific racial and/or ethnic groups. Ethnic and/or racial origin is very rarely reported in cases received by Neurim and its partner companies (recorded on the global safety database), and no Slenyto cases included this.

Given that more than half of all Slenyto usage is in CCI [redacted] and a further CCI [redacted], it is most likely that the majority of patients are Caucasian. The only other markets outside of the EEA are Australia, Israel, and Switzerland.

Slenyto EU Off-label Use

Off-label Category	Country(ies)	Source of Information	Comment
Use in children for indications other than insomnia due to ASD and / or Smith-Magenis syndrome	EU-wide.	Spontaneous case reports received by Neurim.	As of the DLP for this RMP, there are CCI cases in the global safety database of Slenyto being used other than for its authorized indications relevant to the DLP. The most frequently reported of these include ADHD and ASD without specifying insomnia due to it. Other less-frequently reported indications included Angelman syndrome, communication disorder, developmental delay, foetal alcohol syndrome, intellectual disability, language disorder, neurodevelopment disorder psychomotor hyperactivity, Rett syndrome, speech development disorder and tuberous sclerosis complex or unspecified congenital anomalies.
Use in adults aged 18-64 years	EU-wide.	Spontaneous case reports received by Neurim.	There are CCI cases in the global safety database of use in adults aged 18-64 years. Of these, CCI are in adults aged 18-25 years.
Use in the elderly (>65 years)	EU-wide.	Spontaneous case reports received by Neurim.	There are CCI cases in the global safety database of use in the elderly (>65 years)
Use in infants (<24 months)	EU-wide	Spontaneous case reports received by Neurim	There are CCI cases in the global safety database of use in patients aged <24 months.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; ASD = Autism Spectrum Disorders; EU = European Union

Data source: On file.

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

There appears to be minimal potential for misuse for illegal purposes. There are no cases of misuse for illegal purposes to date in the post-marketing database of Slenyto or of the reference product Circadin.

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- None.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None.

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each European Union Member state where the product is authorized):

- None.

Known risks that do not impact the risk-benefit profile:

- None.

Other reasons for considering the risks not important:

- None.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important potential risk 1: Delay of sexual maturation and development

Risk-benefit impact: Melatonin delays sexual development in the rat in a transient and reversible manner, which corroborates the absence of any sustained effects of melatonin in the repeat dose, reproduction and juvenile non-clinical toxicology applicant sponsored studies. No effects on sexual development were measured in the clinical study following up to 24 months treatment. The applicant will continue to examine any relevant post marketing safety reports carefully and if the RTU results available in April 2019 indicate that there is a need for another registry, the applicant will sponsor a non-interventional post authorization safety study (PASS) to monitor and assess changes in pubertal development (e.g. onset of puberty or final height) during the post-marketing period. The study design will be according

to EMA guidelines, Guideline on good pharmacovigilance practices (GVP), Module VIII – Post-authorisation safety studies (PASS).
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf

Missing Information 1: Use in pregnancy and lactation

Risk-benefit impact: Transfer via breast milk and/or physiological excretion of melatonin into maternal milk have been shown in different animal species and humans; additionally melatonin crosses the placenta and shows rhythmic variations in breast milk, in parallel with plasma, in both humans and goats. As there is very little experience of the use of Slenyto or the reference product, Circadin, in human pregnancy and lactation, the SmPC advises that the use of Slenyto in this population would be done after discussing this with the physician. Any reported pregnancies will be monitored appropriately through routine pharmacovigilance practices.

Missing Information 2: Long-term safety in children (more than 2 years)

Risk-benefit impact: Long-term data up to 2 years is available and demonstrate that the product is safe in this population for this length of time. The reference product is used off-label for longer periods and also monitored under the RTU in France up to 3 years at least – this data will be available on April 2019. The SmPC Section 4.2 advises that data is available for up to 2 years' treatment.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable – no new safety concerns or reclassification of existing concerns were made to this current proposed RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

None.

SVII.3.2 Presentation of the Missing Information

Table 10 Missing Information

Missing Information	
Missing Information: Use in pregnancy and lactation	
Evidence Source	Transfer via breast milk and/or physiological excretion of melatonin into maternal milk have been shown in different animal species and humans; additionally, melatonin crosses the placenta and shows rhythmic variations in breast milk, in parallel with plasma, in both humans and goats.
Anticipated risk/consequence of the missing information	As there is very little experience of the use of Slenyto or the reference product, Circadin, in human pregnancy and lactation, the SmPC warns against use of Slenyto in this population.
Missing Information: Long-term safety in children (more than 2 years)	
Evidence Source	The pivotal clinical study in the pediatric population was 2 years long, Under the RTU, data was monitored for use of Circadin up to 6 mg /day in pediatric patients for up to 55 months. The results of this registry are now available.
Anticipated risk/consequence of the missing information	The SmPC under section 4.2 indicates that “Data is available for up to 2 year’s treatment”.

Abbreviations: SmPC = Summary of Product Characteristics
Data source: On file.

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 11 Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy/lactation Long-term safety in children (> 2 years)

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires for use during pregnancy and lactation:

None.

Other Forms of Routine Pharmacovigilance Activities for use during pregnancy and lactation:

None.

III.2 Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimization Measures

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 12 Ongoing and Planned Additional Pharmacovigilance Studies

StudyStatus	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
None	Not applicable	Not applicable	Not applicable	Not applicable

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 13 Planned and On-going Post-authorization Efficacy Studies that are Conditions of the Marketing Authorization or that are Specific Obligations

StudyStatus	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorization				
None				

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 Routine Risk Minimization Measures

Table 14 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Measures
Important Missing Information	
Use in pregnancy and lactation	Routine risk communication: SmPC and PL warnings. Indication in Section 4.6 of the SmPC (Fertility, pregnancy, and lactation) that there is not sufficient data relating to the use of Slenyto during breastfeeding and pregnancy. Inclusion of warning in the package leaflet that “If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine”.
Long-term safety in children (> 2 years)	Routine risk communication: SmPC warnings Indication in Section 4.2 of the SmPC that “Data is available for up to 2 year’s treatment”.

Abbreviations: PL = package leaflet; SmPC = summary of product characteristics.
Data source: On file.

V.2 Additional Risk Minimization Measure

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table 15 Summary of Risk Minimization Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Missing Information		
Use during pregnancy and lactation	Routine risk minimization measures: Indication in Section 4.6 of the SmPC (Fertility, pregnancy, and lactation) that there is not sufficient data relating to the use of Slenyto during breastfeeding and pregnancy. Inclusion of warning in the package leaflet that "If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine" Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Reports describing pregnancy are followed up and documented until the outcome is known. Additional pharmacovigilance activities: None.
Long-term safety in children (> 2 years)	Indication in Section 4.2 of the SmPC that "Data is available for up to 2 year's treatment"	Monitor any relevant post marketing safety reports. Reports related to long-term use would be specifically followed up. Final report of the RTU has now been submitted.

Abbreviations: SmPC = summary of product characteristics.
Data source: On file.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Slenyto 1 mg and 5 mg prolonged-release tablets (melatonin)

This is a summary of the RMP for Slenyto 1 mg and 5 mg prolonged release tablets. The RMP details important risks of Slenyto, how these risks can be minimized, and how more information will be obtained about Slenyto's risks and uncertainties (missing information).

Slenyto's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Slenyto should be used.

This summary of the RMP for Slenyto should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Slenyto's RMP.

I. The Medicine and What it is Used For

Slenyto is authorized for:

- treatment of insomnia in children and adolescents aged 2-18 years with Autism Spectrum Disorder (ASD) and/ or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient,
- treatment of insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been insufficient (see SmPC for the full indication).

It contains melatonin as the active substance and it is given by oral administration.

Further information about the evaluation of Slenyto’s benefits can be found in Slenyto’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Slenyto, together with measures to minimize such risks and the proposed studies for learning more about Slenyto's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Slenyto is not yet available, it is listed under 'missing information' below.

IIA List of Important Risks and Missing Information

Important risks of Slenyto are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Slenyto. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 16 List of Important Identified/Potential Risks/Missing Information

List of Important Risks and Missing Information	
Important Identified Risks	None
Important Potential Risks	None
Missing Information	Use in pregnancy and lactation Long-term safety in children (> 2 years)

IIB Summary of Important Risks/Missing Information

Table 17 Summary of Important Identified/Potential Risks/Missing Information

Missing Information: Use in pregnancy and lactation	
Evidence for Linking the Risk to the Medicine	Transfer via breast milk and/or physiological excretion of melatonin into maternal milk have been shown in different animal species and humans; additionally melatonin crosses the placenta and shows rhythmic variations in breast milk, in parallel with plasma, in both humans and goats.
Risk Factors and Risk Groups	Pregnant and lactating women
Risk Minimization Measures	Routine risk minimization measures: Indication in Section 4.6 of the SmPC (Fertility, pregnancy, and lactation) that there is not sufficient data relating to the use of Slenyto during breastfeeding and pregnancy. Inclusion of warning in the package leaflet that "If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine". Additional risk minimization measures: None.
Additional Pharmacovigilance Activities	Reports describing pregnancy shall be followed up and documented until the outcome is known. Additional pharmacovigilance activities: None.
Missing Information: Long term safety in children (>2 years)	
Evidence for Linking the Risk to the Medicine	There is no official data with the product for a duration longer than 2 years.
Risk Factors and Risk Groups	The target population and children that will be treated off label.
Risk Minimization Measures	Indication in Section 4.2 of the SmPC that "Data is available for up to 2 year's treatment"
Additional Pharmacovigilance Activities	Monitor any relevant post marketing safety reports. Reports related to long-term use would be specifically followed up. The final report of the RTU has now been submitted.

Abbreviations: SmPC = summary of product characteristics.
Data source: On file.

IIC Post-Authorization Development Plan

IIC.1 Studies Which are Conditions of the Marketing Authorization

None.

IIC.2 Other Studies in Post-Authorization Development Plan

None.

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Annex 4: Specific Adverse Event Follow-Up Forms

No specific adverse event follow-up forms are in use.

Annex 6: Details of Proposed Additional Risk Minimization Measures

Not applicable.