30 January 2025
EMA/119604/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Slenyto

International non-proprietary name: Melatonin

Procedure No. EMEA/H/C/004425/II/0028

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ASD	Autism Spectrum Disorder
AUC	Area under the concentration-time curve
$AUC_{0\text{-}8hr}$	Area under the concentration-time curve from time zero to 8 hours
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
CI	Confidence interval
C_{max}	Maximum concentration
CREB	cAMP Responsive Element-binding
CSDI	Composite Sleep Disturbance Index
DSM	Diagnostic and Statistical Manual
DSPD	Delayed Sleep Phase Disorder
FAS	Full analysis set
IR	Immediate release
LSE	Longest sleep episode
MAH	Marketing Authorisation Holder
MMRM	Mixed-effects model for repeated measures
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PKA	Protein Kinase A
po	Oral administration
PPP	Per protocol population
PR	Prolonged release
PrM	Prolonged release melatonin
RCT	Randomized Controlled Trial
SAE	Serious adverse event
SCN	Suprachiasmatic Nucleus
SD	Standard deviation
SDQ	Strength and Difficulties Questionnaire
SE	Standard error
SEM	Standard error of the mean
SL	Sleep latency

SmPC	Summary of Product Characteristics
SMS	Smith-Magenis syndrome
SND	Sleep and nap diary
SWA	Slow wave activity
TD	Typically developing
TEAE	Treatment-emergent adverse event
TST	Total sleep time
WEU	Well-Established Use
WHO-5	World Health Organization Well-Being Index

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, RAD Neurim Pharmaceuticals EEC SARL submitted to the European Medicines Agency on 4 June 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of insomnia in children and adolescents aged 2-18 with Attention-Deficit Hyperactivity Disorder (ADHD), where sleep hygiene measures have been insufficient, based on results from phase III study NEU_CH_7911 and literature. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Tomas Radimersky

Timetable	Actual dates
Submission date	4 June 2024
Start of procedure:	22 June 2024
CHMP Rapporteur Assessment Report	30 July 2024
PRAC Rapporteur Assessment Report	1 August 2024
CHMP Co-Rapporteur Assessment	28 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	11 September 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 September 2024
Request for supplementary information (RSI)	19 September 2024
CHMP Rapporteur Assessment Report	2 January 2025
PRAC Rapporteur Assessment Report	6 January 2025
Updated PRAC Rapporteur Assessment Report	22 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Opinion	30 January 2025

2. Scientific discussion

2.1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone, produced by the pineal gland, which is an regulator the circadian clock and a sleep promoter in humans. Melatonin is thought to act via MT1 and MT2 G-protein coupled receptors in the suprachiasmatic nucleus (SCN) and controls the circadian rhythm. Melatonin deficiency or misalignment is considered a pathophysiological mechanism linked to sleep disturbances in children with neurodevelopmental disorders such as Autism Spectrum Disorder (ASD) and Attention-Deficit Hyperactivity Disorder (ADHD).

The European Union (EU) marketing authorization for Slenyto, a pediatric prolonged release melatonin formulation, was granted on 20 September 2018. Slenyto is currently indicated for the treatment of insomnia in children and adolescents aged 2-18 with ASD and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient.

ADHD is a common disorder among school-aged children. Based on US national representative data, the estimated ADHD prevalence was 10.08% to 10.47% among children and adolescents aged 4 to 17 years from 2017 to 2022. 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. Indeed, seventy percent of children with ADHD experience sleep problems as opposed to twenty to thirty percent in healthy children. 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, lighter sleep, poor sleep quality, fragmented sleep with periods of nightly awakenings due to restlessness or movements, and 30 to 60 minutes of shorter sleep duration. These sleep disorders can also result in daytime sleepiness which negatively affects the children's quality of life and accentuates the observed negative behaviours seen in children with ADHD. To promote sleep in individuals with ADHD sleep education, behavioural interventions, and exogenous melatonin is used. Commonly, IR melatonin is used as a hypnotic, in the dose range of 1-5 mg administered 30-60 minutes prior to desired sleep onset time. Within the EU, several IR melatonin products have been approved for the treatment of insomnia in children and adolescents aged 6-17 years with ADHD via the WEU procedure. In addition, controlled release formulations of melatonin, such as Slenyto and Circadin are, according to the applicant, commonly used for off label treatment of insomnia in children with ADHD (Paton et al., 2024).

The Marketing Authorization Holder (MAH), RAD Neurim Pharmaceuticals EEC SARL (hereafter referred to as Neurim) is currently seeking to expand the approved indications to include the treatment of *insomnia in children and adolescents aged 2-18 years with ADHD, where sleep hygiene measures have been insufficient.*

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Melatonin is a naturally occurring substance which is synthesized in the human body in the brain, retina and pineal gland. As such no studies concerning the environmental risk of melatonin are necessary in accordance with the current guidance on environmental risk assessment (EMES/CHMP/SWP/447/00 corr. 2). Additionally, the presence of melatonin has been demonstrated in bacteria, plants, invertebrates and vertebrates. Indicating that melatonin will be naturally synthesized and potentially excreted into the environment by numerous natural sources, leading to the formation of a natural background concentration. This concentration is unlikely to be significantly influenced by release of melatonin from the use of Slenyto®.

The MAH submitted a signed CV of the environmental expert and justification for not providing environmental risk assessment studies. It is agreed that since the active substance is naturally occurring, the use of Slenyto is unlikely to have a significant effect on environmental levels. The justification is acceptable.

2.2.1. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of melatonin.

2.3. Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

2.3.1. Pharmacokinetics

The pharmacokinetic properties of Slenyto were presented in the initial marketing application. No new PK data or changes related to the pharmacokinetics of Slenyto has been provided within the present application.

2.3.2. Pharmacodynamics

The pharmacodynamic properties of Slenyto were presented in the initial marketing application. No new PD data or changes related to the pharmacodynamics of Slenyto has been provided within the present application.

2.4. Clinical efficacy

2.4.1. Main study

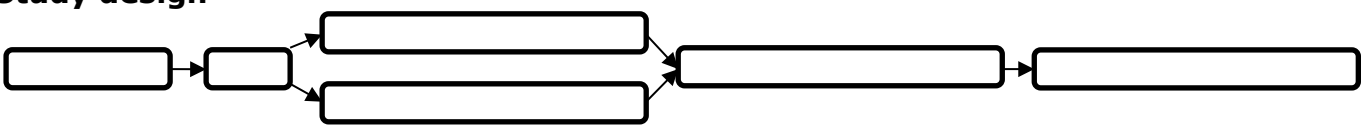
Phase III study NEU_CH_7911

No new efficacy data were submitted. This study was submitted and assessed in the initial marketing authorisation application for Slenyto to support efficacy and safety in children with ASD and/ or Smith-Magenis syndrome. Part of the results of the phase III study have been published (Gringras et al., 2017; Schroder et al., 2019).

Methods

A randomized, placebo-controlled study to investigate the efficacy and safety of Slenyto (referred to as Circadin in the study report) to alleviate sleep disturbances in children with neurodevelopmental disabilities.

Study design



The study population for this study included patients with confirmed history of ASDs (pervasive developmental disorders) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5/4) criteria or International Classification of Diseases 10th Revision (ICD-10) or neurodevelopmental disabilities caused by neurogenetic diseases (Smith-Magenis syndrome, Angelman syndrome, Bourneville's disease [tuberous sclerosis]).

Study participants

A total of 125 children were randomised to the 13-weeks placebo-controlled double blind main phase of the study. The overall mean age of the children included in the study was 8.7 ± 4.15 years (mean ± SD)

with a range 2-17 years. Most patients reported a history of psychiatric disorders (90.4%), with the most common preferred terms being agitation (70.4%) and mood swings (66.4%). Other psychiatric disorders included ADHD (28.8%), autism spectrum disorder (25.6%), sleep disorder (21.6%), anxiety (13.6%), and insomnia (12.0%). Nervous system disorders were reported for 80.0% patients, with the most common preferred terms being somnolence (50.4%), headache (29.6%), autism (14.4%), and speech disorder developmental (11.2%).

Treatments

Slenyto 1 mg prolonged release tablets x 2.

Melatonin starting dose was 2 mg, after 3 weeks optional dose increment to 5 mg. Study duration was 13 weeks. 60 subjects were randomized to Slenyto and 65 subjects received placebo.

Objectives

The phase III study NEU_CH_7911 was conducted to investigate the efficacy and safety of Slenyto (referred to as Circadin) in children with ASD or neurodevelopmental disorders. The efficacy of Slenyto in improving sleep maintenance, sleep latency and additional parameters was assessed in comparison to placebo in a 13-week double-blind treatment period (Gringras et al, 2017, Schroder et al, 2019). The long-term efficacy and safety of Slenyto 2, 5 and 10 mg was assessed during a 91-week open-label extension period (Maras et al, 2018, Malow et al., 2021).

Rapporteur comments

No new data has been provided to support the sought indication. The results of the phase III study, including the subgroup analysis of ADHD patients, were assessed and discussed during the initial application for marketing authorisation of Slenyto.

Outcomes/endpoints

The primary efficacy endpoint was total sleep time, calculated from the Sleep and Nap Diary after 13 weeks of treatment.

Secondary endpoints taken from Sleep and Nap Diary after 13 weeks of treatment included:

- Sleep latency
- Duration of wake after sleep onset
- Number of awakenings
- Longest sleep period

Other secondary efficacy measurements included:

- Sleep disturbance as assessed by the CSDI score
- Social functioning at home, in school, and in community settings as assessed by the CGAS:

The CGAS was administered and completed by the Investigator with the parent/caregiver's input. An overall score was recorded on a scale of 1 to 100.

• Behaviour at home and in school as assessed by the SDQ:

The SDQ was completed by the site coordinators/Investigators with the parents/caregivers, by posing the questions in the questionnaires and filling in the responses given by the parents/caregivers. The SDQ used in this study included supplementary questions to assess impact.

Sample size

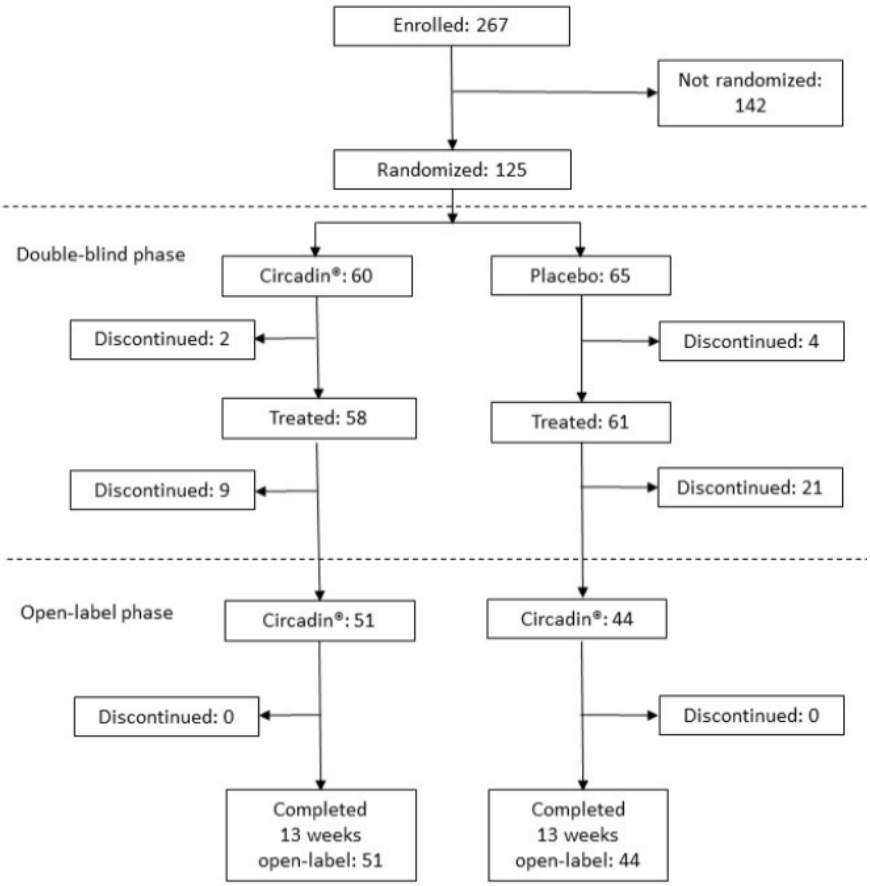
125 randomised subjects were included in the main 13-weeks double blind phase of the study.

N= 60 on Slenyto and N= 65 on placebo.

Results

Participant flow

Overview of the participants in the Phase III study NEU_CH_7911.



Outcomes and estimation

Primary endpoint (TST) in the phase III study NEU_CH_7911

This study met the primary endpoint, demonstrating statistically significant effects of Slenyto 2/5 mg vs. placebo on change from baseline in mean SND-assessed total sleep time (TST) after 13 weeks of double-blind treatment. At baseline, mean TST was 507.6 minutes in the Slenyto and 487.9 minutes in the

placebo group. After 13 weeks of double-blind treatment, participants slept on average 57.4 minutes longer at night with Slenyto compared to 9.1 minutes with a placebo adjusted mean treatment difference Slenyto–placebo of 32.3 minutes (p=0.035, full analysis set [FAS]) (Table 1).

Table 1. SND total sleep time (TST) change from baseline at 13 weeks of double-blind treatment (week 15) for the FAS Set and PPP

Population (N)	Week	Adjusted Treatment Means (SE)		Treatment Difference (SE)	Effect Size	95% CI	p-value
		Slenyto 2 or 5 mg dose	Placebo				
FAS (58, 61)	Week 15	51.03 (10.456)	18.71 (10.816)	32.32 (15.100)	0.43	(2.38, 62.26)	0.035
PPP (44, 44)	Week 15	62.98 (10.999)	21.24 (11.000)	41.74 (15.593)	0.58	(10.73, 72.75)	0.009

Analysis was conducted using a MMRM model with the value at Visit 3 (Week 5) and Visit 4 (Week 15) as the dependent variable, with fixed effects for visit, the mean baseline value, randomized treatment and the mean baseline value and randomized treatment both nested within visit. Effect size is based on Cohen's d.

CI = confidence interval; FAS = full analysis set; MMRM = mixed-effects model for repeated measures; PPP = per protocol population; SE = standard error; SND = sleep and nap diary

N = Patients treated with Slenyto or Placebo.

Secondary endpoints in the phase III study NEU_CH_7911

There was a statistically significant improvement (reduction) in sleep latency with Slenyto compared to placebo after 13 weeks of double-blind treatment (Week 15) as evaluated with the Sleep and Nap diary (SND). Mean (SE) adjusted treatment means of change from baseline in sleep latency in the Slenyto treated group (FAS) was -37.77 (6.82) and for placebo was -12.57 (7.005) minutes (p=0.011, Table 2). Effect size was -0.52 in the FAS as well as the PPP sets.

Table 2. SND sleep latency change from baseline at week 15 for FAS and PPP

Population (N)	Week	Adjusted Treatment Means (SE)		Treatment Difference (SE)	Effect Size	95% CI	p-value
		Slenyto 2 or 5 mg dose	Placebo				
FAS (58, 61)	Week 15	-37.77 (6.816)	-12.57 (7.005)	-25.20 (9.787)	-0.52	(-44.61, -5.80)	0.011
PPP (44, 44)	Week 15	-40.42 (7.783)	-14.04 (7.783)	-26.37 (11.022)	-0.52	(-48.29, -4.46)	0.019

*Analyzed using a MMRM model with the value at Visit 3 (Week 5) and Visit 4 (Week 15) as the dependent variable, with fixed effects for visit, the mean baseline value, randomized treatment and the mean baseline value and randomized treatment both nested within visit. Effect size is based on Cohen's d.

CI = confidence interval; FAS = full analysis set; MMRM = mixed-effects model for repeated measures; PPP = per protocol population; SE = standard error; SND = sleep and nap diary

The sleep maintenance parameter, longest sleep duration, as assessed by the SND after 13 weeks of double-blind treatment (a secondary outcome variable), also improved with Slenyto compared to placebo. Mean (SE) adjusted treatment means of change from baseline in longest sleep period in the Slenyto treated group (FAS) was 71.99 (14.76) vs. 30.01 (15.49) minutes with placebo (p=0.053; Table 3). Effect sizes of the treatment (over placebo) were 0.41 in the FAS and 0.54 in the PPP sets.

Table 3. SND longest sleep period change from baseline at week 15 for the FAS and PPP

Population (N)	Week	Adjusted Treatment Means (SE)		Treatment Difference (SE)	Effect Size	95% CI	p-value
		Slenyto 2 or 5 mg dose	Placebo				
FAS (58, 61)	Week 15	71.99 (14.763)	30.01 (15.492)	41.98 (21.431)	0.41	(-0.57, 84.53)	0.053
PPP (44, 44)	Week 15	90.10 (16.224)	34.92 (16.432)	55.18 (23.102)	0.54	(9.16, 101.20)	0.019

*Analyzed using a MMRM model with the value at Visit 3 (Week 5) and Visit 4 (Week 15) as the dependent variable, with fixed effects for visit, the mean baseline value, randomized treatment and the mean baseline value and randomized treatment both nested within visit. Effect size is based on Cohen's d.

CI = confidence interval; FAS = full analysis set; MMRM = mixed-effects model for repeated measures; PPP = per protocol population; SE = standard error; SND = sleep and nap diary.

ADHD subgroup in the phase III study NEU_CH_7911

At baseline, 28.8% patients were diagnosed with ADHD before study initiation. The primary (total sleep time, TST) and secondary sleep parameters (sleep latency, SL) were evaluated in the sub-population with ADHD during the double-blind period of the phase III study.

Table 4. Sleep parameters:

All ages **Sleep Parameters (13 weeks Double-blind)**					
N	**Variable**	**Group**	**V4-V2**	**Treatment Difference**	**p-value[1]**
44	TST (mins)	**Slenyto**	51.175	43.728	0.040
34		**Placebo**	7.447		
44	SL (mins)	**Slenyto**	-39.975	-35.916	0.006
34		**Placebo**	-4.059		

[1] T-test

Following the t-test analysis, there was a significant effect on both TST and SL versus placebo after 13 weeks double-blind treatment in the subgroup of children with ADHD (and ASD).

The MAH evaluated the clinical relevance of the effect in a responder analysis using improvement in duration of mean TST by 45 minutes or more as a criterion of clinical response (Gringras et al, 2017). The percentage of TST responders after 13 weeks of double-blind treatment in the Slenyto group was 41%, compared to 23% in the placebo group.

In the subgroup of children with ADHD below 6 years of age, there was no statistically significant effect on sleep parameters (TST and SL) likely due to the small sample size (n=9-11/group). However, it can be observed that the effect sizes were similar to the efficacy in the total population.

Supportive studies (literature data)

To support the sought indication, the MAH has also provided several published randomized placebo-controlled studies investigating the effect of melatonin in children with sleep disturbances (insomnia) ADHD (van der Heijden et al., 2007; Weiss et al., 2006; Jan et al., 2000; Mostafavi et al., 2012; Mohammadi et al., 2012; Gringras et al., 2017) and long term follow up studies (mean time to follow up 2.2, 3.7 and 2 years respectively) (Jan et al., 2000; Hoebert et al., 2009; Malow et al., 2021; Maras et al., 2018).

Since several IR melatonin formulations have been approved for use in children with ADHD based on bibliographic WEU procedures in the EU, most published studies include IR melatonin products, which is a different formulation compared to the prolonged release formulation applied for in the present application. The study by van der Heijden et al.,2007 is considered a main (pivotal) study supporting efficacy of IR melatonin in children 6 to 12 years with ADHD. In general, IR melatonin medicinal products are approved in the EU for use in children and adolescents from 6 to 17 years of age with ADHD which is in agreement with the patient population in published literature (e.g., van der Heijden et al., 2007). Further, the study by Gringas et al., 2017 is a large published randomised placebo-controlled study evaluating efficacy of PR melatonin in children with ASD and ADHD, and this published study summarises the results of the clinical phase III study NEU_CH_7911 (Gringas et al 2017).

Table 5 summarise the submitted literature data on melatonin in children with ADHD.

Table 5. Summary of RCT trials and follow up in children with ADHD

	Melatonin	**Placebo**	**Analysis**	**Comment**
van der Heijden et al. 2007 (the Netherlands) RCT (3 or 6 mg daily for 4 weeks)				
Treatment:	3-6 mg IR melatonin No behavioural intervention No Stimulant	placebo No behavioural intervention No Stimulant	All	
Age and condition	ADHD and chronic sleep-onset insomnia age 6-12 years			
Completed and analysed	n=53	n=52	n=105	
Primary sleep outcomes				
Actigraph-derived sleep onset[a] (±SD)	–26.9±47.8 minutes mean change compared with baseline	+10.5±37.4 minutes mean change compared with baseline	p<0.0001 between groups; no mean difference reported	

	Melatonin	Placebo	Analysis	Comment
Actigraph-derived total time asleep (±SD)	+19.8±61.9 minutes mean change compared with baseline	–13.6±50.6 minutes mean change compared with baseline	p=0.01 between groups; no mean difference reported	
Parent-reported difficulty falling asleep (averaged over 7 days on a scale of 1 [not difficult] to 5 [very difficult])	–1.2±1.3 points (35% of baseline)	–0.1±0.8 points (4.3% of baseline)	p<0.0001 between groups; no mean difference reported	
Other outcomes				
Actigraph-derived sleep latency[b] (±SD)	–21.3±33.0 minutes mean change compared with baseline	+3.0±31.7 minutes mean change compared with baseline	p=0.001 between groups; no mean difference reported	
Dim light melatonin onset (±SD)	–44.4±67.9 minutes mean change compared with baseline	+12.8±60.0 minutes mean change compared with baseline	p<0.0001 between groups; no mean difference reported	
Behaviour, cognition, and quality of life			There was no significant effect on behaviour, cognition, and quality of life.	
Long term follow up	Open label mean follow up 3.7 years (n=101) showed sustained effects of exogenous melatonin therapy in children with ADHD and chronic sleep onset insomnia without stimulants.			
Weiss et al. 2006 (Canada) 10-day sleep hygiene followed by crossover placebo controlled trial (5mg daily for 10 days) in MOH treated children with ADHD				
Treatment:	5 mg IR melatonin Add on to Behavioural intervention and Stimulant	placebo Add on to Behavioural intervention and Stimulant	All	

	Melatonin	Placebo	Analysis	Comment
Age and condition	ADHD and chronic sleep-onset insomnia age 6.5-14.7 years			
Analysed	n=19	n=19	19 (crossover trial design)	
Outcomes				
Primary outcome: Sleep onset latency[c] (±SD) **(measured by parent completed somnolog)**	Mean 46.4±26.4 minutes	Mean 62.1±26.6 minutes	Effect size 0.6 Absolute difference 15.7 minutes ($p<0.01$)	
Secondary outcome **Sleep onset latency (±SD)** **(measured by actigraph)**	Not reported	Not reported	Melatonin reduced sleep onset latency by 16 minutes compared with placebo ($p<0.01$)	
Mohammadi et al. 2012 placebo controlled trial (3-6mg daily for 8 weeks) in ADHD				
Treatment:	3-6 mg IR melatonin Add on to Stimulant	placebo Add on to Stimulant	All	
Age	ADHD age 7-12 years			
Analysed	n=26	n=24	50	
Primary outcome				
Total sleep duration (measured by parent-completed SDSC sleep questionnaire)	Mean duration increased from 8.0 to 8.51 h	Mean duration decreased from 8.77 to 8.27 h	p=0.197 no significant difference between groups; no mean difference reported	
Sleep onset latency **(measured by parent completed SDSC sleep questionnaire)**	Mean latency increased from 21.37 to 26.37 minutes	Mean duration decreased from 23.15 to 17.96 minutes	p=0.267 no significant difference between groups; no mean difference reported	

	Melatonin	Placebo	Analysis	Comment
Behaviour-ADHD scores			No significant differences between the groups	
Mostrafavi et al Height and weight growth of children	Mean height (138.28±16.24 vs. 141.35±16.78; P=0.000) and weight (36.73±17.82 vs. 38.97±17.93; P=0.005) were significantly increased compared to baseline with melatonin but not placebo			
Jan et al. 2000 (Canada) RCT crossover trial who failed on IR-melatonin (previous IR dose or half dose of Circadin daily for 22 days) in 42 children with Neurodevelopmental disorders (7 of the 42 had ADHD)				
Treatment:	2-10 mg Circadin (Average 4.2 mg)	5-25 mg IR melatonin (Average 7 mg)	All	
Age and condition	ADHD (7 of 42) age 7-12			
Analysed in RCT	n=16	n=16	16 (crossover trial design)	
Primary outcome **Sleep onset latency[c] (±SD)** **(measured by parent completed somnolog)**	Prolonged release melatonin was more useful for sleep maintenance.	IR melatonin was most effective when there was only delayed sleep onset,	Mean Values not given	
Long term follow up	Open label mean follow up 2.2 years (n=42) showed sustained effects of prolonged release melatonin therapy final dose 5.7 mg in children with ADHD and chronic insomnia. Prolonged release melatonin was useful for sleep maintenance and at a lower dose			
Gringras et al. 2017 (EU and USA) RCT (2 or 5mg or placebo daily for 13 weeks) 28.8% of participants had ADHD and 10.4% used stimulants				
Treatment:	2-5 mg Slenyto Behavioural intervention Add on to Stimulant in some	placebo Behavioural intervention Add-on to Stimulant in some	All	
Age and condition	ASD with and without ADHD (36 of 125 had ADHD) age 2-17 years			
Completed and analysed	n=58	n=61	n=119 of 125	

	Melatonin	Placebo	Analysis	Comment
Primary sleep outcomes				
Total sleep time measured by caregivers' Sleep and Nap Diary (SND)	Participants slept on average 57.5 minutes longer at night with Slenyto	participants slept on average 9.14 minutes longer at night with placebo	adjusted mean treatment difference Slenyto-placebo -32.43 minutes; p = .034).	MMRM analysis including ADHD comorbidity as a factor demonstrated equal improvements in participants with and without ADHD (adjusted mean difference 32.92 minutes and 32.96 minutes respectively).
Sleep onset latency measured by caregivers' Sleep and Nap Diary (SND)	Sleep latency (SL) decreased by 39.6 minutes on average with Slenyto	Sleep latency (SL) decreased by 12.5 minutes with placebo –	Adjusted mean treatment difference -25.30 minutes; p = .011) without causing earlier wakeup time	
Other outcomes				
Behaviour reported by caregivers (SDQ)	Slenyto treatment resulted in significant improvement in externalising but not internalizing behaviour (Strengths and Difficulties questionnaire; SDQ) compared to placebo (p = 0.021) with clinically-relevant improvements in 53.7% of Slenyto-treated versus 27.6% of placebo-treated subjects (p = 0.008).			MMRM analysis including ADHD comorbidity as a factor demonstrated equal improvement in SDQ in participants with and without ADHD comorbidity. (adjusted mean difference of- 0.89 and -1.4 units respectively)
Parent quality of life reported by WHO-5	Caregivers' quality of life also improved with Slenyto versus placebo (p = 0.010) and correlated with the change in total SDQ (p = 0.0005).			
Long term follow up	Open label mean follow up 2 years (n=90) showed sustained effects of exogenous Slenyto therapy in children with ADHD and insomnia. No delays in Growth and puberty were observed.			

Abbreviations: n, number of patients; RCT, randomised controlled trial; SD, standard deviation.
[a] Sleep onset is the clock time at the point when the child falls asleep.
[b] Sleep latency is the time from lights out until sleep onset.
[c] Sleep onset latency is the time from when the child was put to bed until sleep onset.

In a published phase III GCP placebo controlled RCT 125 subjects aged 2-17 with Autism spectrum disorder (ASD) and sleep maintenance and/or initiation problems who failed to improve on behavioural intervention alone, received 2 or 5 mg Slenyto or placebo for 13 weeks (Gringras et al., 2017). This

published literature summarizes the results of study NEU_CH_7911, presented in Section 4.1. In this study 28.8% participants (n=36) had diagnosis of ADHD and 77% of the children (n=96) had abnormal hyperactivity behaviour scores; prior ADHD treatment was reported by 10.4% of participants (n=13). By the end of the 13 weeks treatment, children slept on average 57.50 minutes longer in the Slenyto-treated (n=52), compared to 9.14 minutes in the placebo treated group and fell asleep on average 39.6 minutes faster in the Slenyto-treated, compared to 12.51 minutes in the placebo treated group (n=48). Analysis of the covariance taking ADHD as a factor indicated no difference in response between Slenyto treatment resulted in significant improvement in externalising behaviour (Strengths and Difficulties questionnaire; SDQ) compared to placebo ($p = 0.021$) with clinically relevant improvements in 53.7% of Slenyto-treated versus 27.6% of placebo-treated subjects ($p = 0.008$) (Schroder et al., 2019). Caregivers' quality of life also improved with Slenyto versus placebo ($p = 0.010$) and correlated with the change in total SDQ ($p = 0.0005$) (Schroder et al., 2019). Hence, Slenyto alleviates insomnia-related difficulties, particularly externalising behaviour in the children, subsequently improving caregivers' quality of life. The same effects on sleep duration, latency and behaviour were seen on the subpopulation with hyperactivity and inattention at baseline (77% of the total population) and in 20 children aged < 6 years old – demonstrating efficacy in the target population with ADHD and specifically in the younger patient population subjects with insomnia who had ADHD and those without ADHD diagnosis (Gringras et al., 2017).

Jan et al. (Jan et al., 2000) compared the effects of IR melatonin and Circadin (PR melatonin) on children and adolescents age 4-21 years with neurodevelopmental difficulties and sleep maintenance problems; 7 of the 42 children had ADHD. The average final Circadin dose in the 42 patients was 5.7 mg (2–12 mg) and average final IR-melatonin dose was 7 mg (2-15 mg). The average follow-up duration (Circadin only) was 2.2 years. This study showed that the IR melatonin was most effective when there was only delayed sleep onset, but prolonged release formulations were more useful for sleep maintenance.

van der Heijden et al. (van der Heijden et al., 2007) examined 105 children aged 6-12 years with ADHD and coexisting insomnia who did not receive ADHD medications nor behavioural intervention. In their study IR melatonin supplementation was used at a dose of 3 mg or 6 mg for 4 weeks. IR melatonin advanced circadian rhythms of sleep-wake and endogenous melatonin and shortened sleep latency in children with ADHD and chronic sleep onset insomnia. Sleep onset advanced on average by 26.9 min in the group on IR melatonin and delayed by 10.5 min in the placebo group. Total time asleep increased by 19.8 min in the group on IR melatonin compared to 13.6 min decrease in the placebo group. No effect was found on problem behaviour, cognitive performance, or quality of life (van der Heijden et al., 2007).

A recent systematic review on the use of prolonged-release melatonin (PR melatonin) in circadian medicine concluded that overall, PR melatonin in circadian medicine is an effective chronopharmaceutical for restoring the sleep-wake rhythm in patients with insomnia disorder. This efficacy may also extend to sleep disorders associated with mood, neurodevelopmental including ADHD and neurocognitive disorders, suggesting a further potential role in insomnia associated with various organic diseases (Del casale et al, 2024).

2.4.2. Discussion on clinical efficacy

Slenyto is a prolonged-release formulation containing 1 or 5 mg of melatonin which is currently approved in the EU for the 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. In the present variation type II procedure, the MAH applied for the following new indication including children and adolescents aged 2-18 years with ADHD.

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

The intended indication is primarily supported by a subgroup analysis of the phase III study [NEU_CH_7911] including children with ADHD diagnosis together with ASD. This study was submitted to support initial marketing authorisation of Slenyto and the results of the phase III study has been assessed in detail previously.

Whereas the PR formulation of Slenyto showed beneficial effects in terms of increasing total sleep time and reducing sleep latency in the sub-population with ADHD comorbidity (n=78) in the clinical phase III study, the CHMP concluded during the initial MAA that the proposed indication wording in the SmPC document stating "*…autism spectrum disorder (ASD)… with or without ADHD comorbidity*" was not acceptable since this information was not considered to be of importance to the treating physician.

From a methodological and statistical point of view, a subgroup analysis has, in general, several limitations where findings in sub-group analysis often constitute exploratory and hypothesis-generating findings, rather than conclusive data. However, the overall outcome of the main phase III study on both primary and secondary endpoints was positive, showing therapeutic benefits of Slenyto in treatment of insomnia in children with ASD and ADHD. Thus, the performed subgroup analysis is considered acceptable. However, in the first round of the present procedure the provided efficacy data including a sub-group analysis of the previously submitted main study NEU_CH_7911 as well as supportive literature studies were overall not considered sufficient to support efficacy claims of Slenyto in the new therapeutic indication of treatment of insomnia in children and adolescents aged 2-18 years with ADHD, where sleep hygiene measures have been insufficient.

To justify the proposed new indication of treatment of insomnia in children with ADHD, the MAH has summarised available field of knowledge of melatonin in sleep disturbances in neurodevelopmental disorders including ADHD and ASD. The response included published clinical data on the effects on sleep of IR melatonin in ADHD as well as ASD, and in some cases also prolonged-release melatonin, RWE data and case reports of PR melatonin in children with ADHD.

In addition to the results of the supportive phase III clinical study with Slenyto, the MAH presented separate published literature studies showing effects of IR melatonin in the treatment of insomnia in children with ADHD as well as in children with ASD. MAH also considers the off-label use of PR melatonin products (Slenyto/Circadin) in children and adolescents with ADHD and sleep disturbances supports the extension of the indication of Slenyto to treat insomnia in children and adolescents aged 2-18 with ADHD. The off-label use of PR melatonin to treat insomnia in children with ADHD could be considered supportive information. One published phase III placebo-controlled study with PR melatonin has been submitted. The RCT published by Gringras et al., 2017 involved 125 subjects aged 2-17 years with ASD and concomitant ADHD and sleep disturbances administered Slenyto or placebo for 13 weeks. This published study summarises the results of previously submitted phase III trial NEU-CH_7911. The authors compared the efficacy of 2 mg PR melatonin with placebo, showing a significant PR melatonin effect in increasing sleep duration (by an average of 57.5 minutes) and reducing latency time (by an average of 39.6 minutes).

Patients not experiencing any significant improvement at 3 weeks received a dosage increase from 2 mg to 5 mg, with benefits regarding up to 50% of the subsample. The effects of PR melatonin were not modified by comorbidity such as ADHD and the effects were maintained throughout the observation period.

Whereas the randomised placebo-controlled study conducted with IR melatonin in 105 children aged 6-12 years with ADHD and sleep disturbances (van der Heijden et al., 2007) has some limitations (e.g., no effect was shown on behaviour, cognition or quality of life), it is considered a main clinical study which has previously been used to support approval of IR melatonin in the treatment of insomnia in children with ADHD in several WEU procedures in the EU/ESS. Since IR formulations of melatonin are different from the PR formulation of Slenyto applied for in the present application, the MAH has provided a discussion of why extrapolation of IR data to a PR product is feasible. In line with the CHMP opinion in a recent variation type II procedure for Slenyto (EMA/CHMP/PRAC/70915/2024), the MAH argues that the mechanism of action of melatonin on sleep latency, sleep maintenance and total sleep time is independent of the background disorder. This implies that any patient with a neurodevelopmental, including ADHD and ASD, with sleep disturbances associated with aberrant diurnal melatonin secretion patterns and/or insufficient nighttime melatonin secretion may benefit from prolonged-release melatonin.

Based on review of totality of data presented in the Applicants response, including comparable findings of IR/PR melatonin on sleep latency in children with ASD, the results with PR melatonin showing improved sleep latency, sleep maintenance and total sleep time in children with ASD (with and without ADHD) together with external data of IR melatonin on sleep disturbances in children with ADHD or ASD, and that the mechanism of action of melatonin is independent of the neurodevelopmental background disorder, clinical efficacy of PR melatonin in children with ADHD is expected. Given that melatonin has a well-known general effect of melatonin on sleep and the diurnal sleep-wake cycle and the consistent effects of PR melatonin on sleep onset latency and total sleep time in children with neurodevelopmental disorders, it appears reasonable to extend the indication of PR melatonin from the approved treatment of insomnia in ASD to treatment of insomnia in children with ADHD.

The MAH seeked approval for the use of melatonin in children with ADHD from 2-18 years. Initially the MAH was also asked to justify the proposed age range of 2-18 years in children with ADHD. Whilst the inclusion criteria in the main phase III study allowed subject between 2 and 17 years to participate, the mean age of the children were approximately 9 years ± 4 years (mean ± SD) in this study. Further, due to small study size (n= 9-11 per group), there was no significant effect of PR melatonin in children below 6 years of age with ADHD concomitantly to ASD, albeit the effect sizes was similar to the efficacy in the total population. Moreover, based on published efficacy data on IR melatonin in children with ADHD (e.g., van der Heijden et al., 2007), approved IR melatonin products (through WEU procedures) include ADHD patients aged 6-17 years. There is no relevant clinical efficacy data submitted to support the use of melatonin in children below 6 years of age with ADHD. In addition, a detailed assessment of an ADHD diagnosis is challenging in young children of 5-6 years of age. Overall, the Applicants justification to approve the proposed age range including children from 2 to 18 years with ADHD is not supported. Thus, the posology section 4.2 of the SmPC was revised accordingly (i.e., including children and adolescents aged 6 to 17 years with ADHD)**.**

The proposed posology in children with ADHD and insomnia includes the maximum dose of 10 mg of Slenyto. However, no data on the 10 mg dose of PR melatonin has been presented in placebo-controlled studies in children with ADHD. Of note, the dosing regimen of IR melatonin products in paediatric population is generally in the range of 1-5 mg, which is based on the dosing regimen used in clinical literature studies. In the first round, the MAH was asked to discuss the relevance of a maximum dose of 10 mg in the ADHD indication. No new or unexpected safety issues are likely when using the 10 mg dose in children with ADHD, since this dose has already been approved for Slenyto in the treatment of insomnia in children with ASD and/or neurogenetic diseases. Common general side effects of Slenyto

include drowsiness, fatigue and hangover effects as stated in the SmPC. Whereas the lowest efficacious dose of melatonin should be used, the 10 mg dose may be of benefit for certain patients with ADHD, and the maximum daily dose of 10 mg should only be used when clinically needed.

Following review of the total set of efficacy data presented in the Applicants response, it appears reasonable to extend the indication of PR melatonin from the approved treatment of insomnia in ASD to treatment of insomnia in children with ADHD where sleep hygiene measures have been insufficient. However, the age range of children was amended to 6-17 years with ADHD.

2.4.3. Conclusions on the clinical efficacy

No new clinical efficacy studies have been provided with Slenyto. To support clinical efficacy in the new indication of treatment of insomnia in children and adolescents aged 2-18 with ADHD where sleep hygiene measures have been insufficient, the MAH has primarily presented data from a subgroup analysis of the clinical phase III study NEU_CH_7911, which has previously been submitted to support the Slenyto initial marketing authorisation. As supportive information, the MAH has provided literature summaries of IR melatonin and PR melatonin on sleep disturbances in children with ADHD as well as data on off label use of PR melatonin products in children with ADHD.

A subgroup analysis has generally several limitations and results of subgroup analyses are often viewed as exploratory and hypothesis-generating findings, rather than conclusive data. However, since the overall outcome of the main phase III study for both primary and secondary endpoints was positive, showing therapeutic benefits of Slenyto in treatment of insomnia in children with ASD with ADHD comorbidity, the performed subgroup analysis is considered acceptable.

The clinical phase III study with PR melatonin (Circadin/Slenyto) has been published in several articles containing a summary of the results of the main phase III study (e.g., Gringras et al., 2017). Taken together, literature data showed that Slenyto improved significantly sleep latency, total sleep time, sleep maintenance, daytime behaviour and quality of life in children with insomnia and ADHD, which in turn is supportive of the new indication.

Even if the effect sizes in the subgroup with ADHD are of a clinically relevant magnitude, the population is not completely representing the target population, as stated in the proposed indication text in section 4.1 of the SmPC document (i.e., children 2 – 18 years with ADHD), considering that the children were also diagnosed with ASD. However, the MAH has also submitted literature data supporting an effect of melatonin on sleep disturbances in children with ADHD. In addition, a number of IR melatonin formulations have been approved in the EU/EEA through WEU applications to treat insomnia in children and adolescents aged 6-17 years with ADHD. Thus, there is external data with melatonin in children and adolescents aged 6-17 years supporting the results of the clinical phase III study.

Whereas the provided studies support an expected efficacy of melatonin in children with ADHD and insomnia, most literature studies in children with ADHD were performed with IR melatonin formulations (e.g., van der Heijden et al., 2007), which is a limitation since the applied PR melatonin formulation of Slenyto is different compared to IR melatonin products. This issue was initially raised as major objection on clinical efficacy. The MAH was therefore asked to provide a justification for extrapolation of efficacy data between IR melatonin and PR melatonin formulations to support the claims from the literature provided.

Based on review of totality of data presented provided in the Applicants response, including comparable findings of IR/PR melatonin on sleep latency in children with ASD, the results with PR melatonin showing improved sleep latency, sleep maintenance and total sleep time in children with ASD (with and without ADHD) together with external data of IR melatonin on sleep disturbances in children with ADHD or ASD,

and the CHMP opinion that the mechanism of action of melatonin is independent of the neurodevelopmental background disorder, clinical efficacy of PR melatonin in children with ADHD is expected. Given that melatonin has a well-known general effect of melatonin on sleep and the diurnal sleep-wake cycle and the consistent effects of PR melatonin on sleep onset latency and total sleep time in children with neurodevelopmental disorders it appears reasonable to extend the indication of PR melatonin from the approved treatment of insomnia in ASD to treatment of insomnia in children with ADHD.

In the first round of the procedure, the MAH was also asked to justify the proposed age range of 2-18 years in children with ADHD, as part of the efficacy MO. Whilst the inclusion criteria in the main phase III study allowed subject between 2 and 17 years to participate, the mean age of the children were approximately 9 years ± 4 years (mean ± SD) in this study. Further, due to small study size (n= 9-11 per group), there was no significant effect of PR melatonin in children below 6 years of age with ADHD concomitantly to ASD, albeit the effect sizes were similar to the efficacy observed in the total population. Moreover, based on published efficacy data on IR melatonin in children with ADHD (e.g., van der Heijden et al., 2007), approved IR melatonin products (through WEU procedures) include ADHD patients aged 6-17 years. There is no relevant clinical efficacy data submitted to support the use of melatonin in children below 6 years of age with ADHD. In addition, a detailed assessment of an ADHD diagnosis is challenging in young children of 5-6 years of age. Overall, the Applicants justification to approve the proposed age range including children from 2 to 18 years with ADHD is not supported. Thus, the posology section 4.2 of the SmPC was revised accordingly (i.e., including children and adolescents aged 6 to 17 years with ADHD)**.**

2.5. Clinical safety

No new clinical studies on safety have been provided by the MAH. The clinical safety data of Slenyto has already been submitted and assessed in the initial application for marketing authorization of Slenyto in 2018.

Summary of safety data in the main phase III study NEU_CH_7911

In a multicenter phase 3 RCT carried out in the UK, France, Netherlands and USA (Gringras et al., 2017) 125 Children and adolescents aged from 2 years to 17.5 years; with ASD (96.8%), Smith- Magenis syndrome (SMS) (3.2%) whose sleep failed to improve on behavioural intervention alone,were randomized (1:1 ratio), double-blind, to receive Slenyto (2mg escalated to 5mg) or placebo for 13 weeks. In this study 28.8% participants (n=36) had diagnosis of ADHD and prior ADHD treatment was reported by 10.4% of participants (n=13). During the double-blind phase, treatment-emergent AEs (TEAEs) were reported by 51 (85.0%) participants in the Slenyto-treated (202 events) and 50 (76.9%) participants in the placebo-treated group (159 events). Most of these TEAEs were similar between groups and known symptoms in children with ASD (e.g., agitation, mood swings) or generally in children (e.g., upper respiratory tract infection, cough, dyspnea, vomiting). 'Nervous system disorders' were more common in the Slenyto-treated group (41.7% vs 21.5%), difference mainly driven by somnolence and headache which were more common in the Slenyto-treated group. TEAEs judged by the clinician as treatment-related occurred in 12 (20.0%) participants in the Slenyto and 11 (16.9%) in the placebo group (28 and 20 events respectively). Somnolence, an expected AE of Circadin was more commonly reported in the Slenyto than placebo group (Gringras et al., 2017).

During the double-blind phase, severe events were reported by 13 (21.7%) participants in the Slenyto and 13 (20.0%) participants in the placebo group, with similar patterns. One patient in the Slenyto group discontinued due to non-serious AEs (fatigue, agitation, and stereotypy). One patient in the placebo group temporarily discontinued due to 2 SAEs (pneumonia and respiratory tract infection viral) and one

non serious AE (tachypnea). There were no notable differences between Slenyto and placebo for mean changes in blood pressure, pulse rate, respiratory rate, or temperature. Overall, there were no clinically significant differences between Slenyto and placebo for weight, height or BMI. At baseline, the Tanner assessments of pubertal development showed a greater proportion of participants in the placebo group were preadolescent compared to the Slenyto group, reflecting the slightly lower age of participants in the placebo group (mean age 8.4 versus 9.0 years). In the 13-week double-blind phase, there was no apparent difference between Slenyto and placebo in Change from baseline for SD scores of pubic hair, breast and genitalia development. Of 16 participants with a history of epilepsy in the study, only one had experienced a seizure (non-serious absence seizure) and this was during placebo treatment.47

In the long term (2 years follow up) of this study Ninety-five subjects (74.7% males, mean (SD) age 9 (4.24), range 2-17.5 years) received Slenyto (2/5 mg) according to the double-blind phase dose, for 39 weeks with optional dose adjustment (2, 5 or 10 mg/day) after the first 13 weeks (Malow et al., 2021; Maras et al., 2018). Three adverse events were considered "serious" according to standard regulatory definitions, during weeks 13-52 of the study (the first 39 weeks follow-up). These included (1 case each) aggression, oppositional defiant disorder and constipation. All of these events were considered to be "not related" to the study medication by review of the physician investigator and none led to study drug discontinuation. Out of the 95 patients in the follow-up, 74 patients (77.9%) reported a total of 333 treatment emergent adverse events (TEAEs) that emerged during weeks 13-52 of the study – the first 39 weeks of the follow-up. Of these TEAEs 26 events in 17 patients were considered treatment-related by review of the physician investigator: 3 of those in 3 subjects (malaise, headache, and insomnia, (1 case each)) led to study drug discontinuation. There was one patient who temporarily discontinued (interrupted treatment) due to a TEAE (sinusitis) and returned to the study afterwards. The total number of weeks on Slenyto therapy for the 95 patients was 3796 weeks. The most commonly reported TEAES were fatigue (18.9%), vomiting (17.9%), somnolence (16.8%), cough (13.7%), mood swings (13.7%), upper respiratory tract infection (10.5%), headache and rash (8.4% each), dyspnoea (7.4%), constipation, nausea and pyrexia (6.3% each), rhinorrhea, aggression and agitation (5.3% each). Only in 17.9% of patients the TEAEs were considered by the physician investigator to be definitely, probably or possibly related to study medication. Of these, the most commonly reported adverse events were fatigue in 5 patients (5.3%), mood swings in 3 patients (3.2%), irritability, aggression, hangover and somnolence, each in 2 patients (2.1% each). No noticeable changes were found in vital signs at any time-point during the study. Furthermore, there were no differences from baseline in the physical examination. There were small increases in BMI and Z scores (BMI standard deviation of relative weight adjusted for child age and sex, based on the Center for Disease Control (CDC) growth charts) in the Slenyto and placebo groups, with no clinically significant difference between the groups. Mean (SE) z-score increased from baseline by 0.10(0.049) after 26 weeks (p=0.042), 0.11(0.063) after 39 weeks (p=0.077) and 0.20 (0.077) after 52 weeks (p=0.013) of study medication as expected for developing children and adolescents and thus not considered related to the treatment. Mean (SE) BMI increased from baseline 0.44 (0.15) after 39 weeks (p=0.005) and 0.69 (0.18) (p<0.001) after 52 weeks). No TESEs related to weight gain or loss were reported in the study.

Slenyto was generally safe; most frequent treatment-related adverse events were fatigue (5.3%) and mood-swings (3.2% of patients). Eighty children and adolescents (96% ASD) ages 2-17.5 years who completed the double-blind placebo-controlled trial were given 2, 5 or 10 mg Slenyto nightly up to 104 weeks, followed by a 2-week placebo period to assess withdrawal effects. Eighty children and adolescents (96% ASD) ages 2-17.5 years who completed the 39 weeks to follow up were given 2, 5 or 10 mg Slenyto nightly up to 104 weeks, followed by a 2-week placebo period to assess withdrawal effects. Slenyto was generally safe; the most frequent treatment-related adverse events (AE) were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%). The changes in mean weight, height, body mass

index (BMI) and pubertal status (Tanner staging done by a physician) were within normal ranges for age with no evidence of delay in BMI or pubertal development.

Published literature

In this section the MAH refers to several publications using IR melatonin, whereas Slenyto is a PR formulation.

In a RCT in 105 children, van der Heijden et al. (van der Heijden et al., 2007) reported no statistically significant differences between the number of adverse events in the unlicensed IR-melatonin and placebo groups, and for the different doses of melatonin given (3 mg and 6 mg). No adverse events were reported in the placebo group compared with 16 events in the melatonin group reported in10 children. The most common adverse events reported in the melatonin group were headache (3 children, 5.7%), hyperactivity (3 children, 5.7%), dizziness (2 children, 3.8%) and abdominal pain (2 children, 3.8%). No adverse events caused withdrawal from the study and none needed further treatment. Approximately 20% of the 94 children in the long-term follow-up study with unlicensed IR-melatonin (Hoebert et al., 2009) experienced adverse events which they or their parents attributed to melatonin. Mean follow-up time was 3.7 years and mean treatment time was 18 months (range of 1–57 months). No serious adverse events were reported or treatment-related comorbidities. The most common adverse events reported were dizziness (4 children, 4.3%), sleep maintenance insomnia (3 children, 3.2%) and bedwetting (3 children, 3.2%). Of the 94 children, 3 (3%) discontinued melatonin because of adverse events: 1 experienced profuse perspiration; 1 persistent dizziness, visual disturbances, headache and daytime laziness; and 1 headache, abdominal pain, nausea and excessive morning sedation. These adverse events resolved spontaneously after melatonin was stopped.

Weiss et al. (Weiss et al., 2006) found that 20% of all adverse events were reported during melatonin treatment and 23% during placebo treatment. All adverse events were mild or moderate except 1 case of migraine, which was rated as severe. Overall, the unlicensed IR-melatonin used in these studies (3– 6 mg daily) appeared to be well tolerated with only temporary mild to moderate adverse effects reported in the short (up to 4 weeks treatment) and medium term (mean treatment 18 months). No severe adverse effects were reportedly attributable to treatment (van der Heijden et al., 2007; Weiss et al., 2006; Hoebert et al., 2009)

In a RCT carried out in the UK (Appleton et al., 2012; Gringras et al., 2012), 146 children aged from 3 years to 15 years 8 months with neurodevelopmental delay and other conditions (epilepsy or autistic spectrum disorder, or both) were randomised to receive treatment with unlicensed melatonin or placebo for 12 weeks. No children were reported as having ADHD but comprehensive safety data are available. More headaches were recorded as adverse events (14.3% on melatonin compared with 9.2% on placebo) than those recorded in the ADHD trials. The most common adverse events in the melatonin group were: coughing (31.4%), mood swings (22.9%), vomiting (21.4%) and increased excitability (18.6%), which were reported in similar frequencies in the placebo group (no statistical test was undertaken). A weekly seizure diary was completed for children with a pre-existing diagnosis of epilepsy. This showed no deterioration in frequency or severity of seizures. No child without epilepsy developed seizures or had a new diagnosis of epilepsy. Of the 7 serious adverse events, 2 (1 in the melatonin group and 1 in the placebo group; not described) were considered related to the study drug.

Post marketing experience

Safety data was collected from the off-label use of Slenyto/Circadin in ADHD patients covering the time period from 2008 until 30 Decemeber 2023.

Of these cases, some also included ADHD as an indication.

For Slenyto, 73.1% of the cases involved children or adolescents which is consistent with the intended patient population for this product (i.e. aged 2-17 years). Only 1.5% involved adults. However, in around a quarter (25.4%) of the cases, the age of the patient was unknown. Most of the cases with unknown patient ages were received in 2023.

Slenyto cases had proportionately far fewer AEs per case than Circadin (0.3 per case and 0.9 per case respectively). This reflects the fact that many Slenyto cases only report off label use / misuse, medication errors or lack of efficacy and do not include any AEs. The most commonly reported AEs that are unlisted for both products were:

• Diarrhoea: 4 incidences (3 for Circadin, 1 for Slenyto)

• Middle insomnia: 4 incidences (2 for Circadin, 2 for Slenyto)

• Sleep disorder: 4 incidences (3 for Circadin, 1 for Slenyto)

• Anger: 3 incidences (2 for Circadin, 1 for Slenyto)

• Chest discomfort: 3 incidences (2 for Circadin, 1 for Slenyto

Dyspnoea: 3 incidences (3 for Circadin, 0 for Slenyto)

• Pruritus: 3 incidences (3 for Circadin, 0 for Slenyto)

• Tremor: 3 incidences (1 for Circadin, 2 for Slenyto)

• Visual impairment: 3 incidences (3 for Circadin, 0 for Slenyto)

The pattern of reported AEs was generally consistent between the two products with the exceptions of:

• Eye disorders: all 10 eye disorders occurred in patients taking Circadin. These were largely made up of reports of blurred vision (4) or visual impairment (3). Blurred vision is listed in the CCSI for Circadin. Visual impairment is not listed, but it is possible that this is being conflated with visual acuity reduced which is listed in the CCSI.

• General disorders and administration site conditions: for Circadin, there were a total of 22 incidences of AEs distributed across 9 different MedDRA PTs (approximate average of 2 incidences per MedDRA PT). The most frequently reported MedDRA PT was fatigue which is listed in the CCSI for Circadin. For Slenyto, there were just 2 MedDRA PTs with one incidence for each: chest discomfort and screaming. Neither is listed in the SmPC for Slenyto, but screaming would be reasonably anticipated in children with neurodevelopmental disorders.

• Psychiatric disorders: although psychiatric disorders were the most frequently reported AEs for both products, a higher proportion was reported for Circadin than for Slenyto (51.3% vs. 29.7% of all AEs).

For Circadin, 49 incidences of AEs were distributed across 29 different MedDRA PTs (average of 1.7 incidences per MedDRA PT). The most frequently reported MedDRA PTs were aggression (5), insomnia (4), nightmare (4), depressed mood (3) and sleep disorder (3). All of these are listed in the CCSI for Circadin except for sleep disorder, but this is a relatively non-specific term and may reflect the underlying disorders of the patients.

For Slenyto, 20 incidences of AEs were distributed across 13 different MedDRA PTs (average of 1.5 incidences per MedDRA PT). The most frequently reported MedDRA PTs were aggression (4) and agitation (4), both of which are listed in the SmPC for Slenyto.

2.5.1. Discussion on clinical safety

The clinical safety data in the main phase III study NEU_CH_7911 has already been assessed during the initial application for marketing authorisation of Slenyto. The most reported AEs for melatonin are related to headache, gastrointestinal disorders, fatigue, drowsiness, mood or psychomotor or neurocognitive functions. Most AEs were considered mild and of limited duration. The adverse events reported were overall consistent with the safety profile of PR melatonin (Slenyto/Circadin) in children.

Post marketing data are available for Slenyto/Circadin during the period of 2008 to 2023 in ADHD patients. The post-marketing data include patients on Slenyto and Circadin. For Slenyto, 73.1% of the cases involved children or adolescents. Further, post-marketing data included reports associated with off-label use in ADHD patients.

Overall, no new or unexpected safety concerns related to melatonin treatment in children have been identified. The safety profile of PR melatonin seems consistent with the known safety profile as stated in the approved product information.

Overall, melatonin is considered to be well tolerated and no major differences in the safety profile of melatonin are expected when administered to different age groups of children in the approved indication.

2.5.2. Conclusions on clinical safety

Safety for short-term unfavourable effects of melatonin is generally considered mild and well established. Common general side effects of Slenyto include fatigue, drowsiness and hangover effects, per SmPC document.

Long-term safety of PR melatonin (Slenyto/Circadin) has been evaluated in the French RTU study, which was a post-authorisation study (PAM) where clinical safety data were collected from 1st October 2015 to 1st October 2021 in 1038 children 6 to 18 years treated with PR melatonin (Circadin). This RTU study was assessed by the PRAC in 2022 (EMEA/H/C/004425/REC/002.2). The conclusion on the review of the submitted RTU report by the PRAC Rapporteur was that the AEs reported were overall consistent with the safety profile of Circadin, which is authorised for adults. Furthermore, it was concluded that safety concern "Delay of sexual maturation and development" could be removed from the RMP of SLENYTO.

Overall, no new safety risks have been reported for Slenyto in children.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

Table 6. (table SVIII.1): summary of the safety concerns

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)

No changes to the summary of safety concerns have been proposed in this variation. Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

Table 7. (table part III.3.1): On-going and planned additional pharmacovigilance activities

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

Overall conclusions on the PhV Plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

2.7. Risk minimisation measures

Routine risk minimisation measures

Table 8. (table Part V.1): Description of routine risk minimisation 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".

Additional risk minimisation measures

No additional RMM have been proposed.

Overall conclusions on risk minimisation measures (PRAC Rapp)

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.8. Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

2.9. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.9.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Paediatric insomnia in children and adolescents is a widespread problem. The prevalence of paediatric insomnia in children that goes beyond bedtime refusal and night awakenings ranges from 1% to 6% in the paediatric general population. ADHD is a very common disorder among school-aged children (American Psychiatric Association, 2013). Based on US national representative data, the estimated ADHD prevalence was 10.08% to 10.47% among children and adolescents aged 4 to 17 years from 2017 to 2022. 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. Indeed, seventy percent of children with ADHD experience sleep problems as opposed to only twenty to thirty percent in healthy children.

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, lighter sleep, poor sleep quality, fragmented sleep with periods of nightly awakenings due to restlessness or movements) and shorter sleep duration.

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.

3.1.2. Available therapies and unmet medical need

The most commonly prescribed sleep medications to children with ADHD are IR melatonin products. A number of IR melatonin formulations have been approved in the EU/EEA through WEU applications to treat insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

Circadin or Slenyto, are according to the MAH, frequently used off-label in children with ADHD and insomnia. In addition, antihistamines, alpha-adrenergic agonists, antidepressants, antipsychotics, benzodiazapines, and ''Z-drugs'' (zaleplon and zolpidem) may be used to treat insomnia. Most of these medications are being used for their sedative adverse effects rather than for primary effects on sleep/wake mechanisms or hyperarousal.

Circadin, approved for insomnia in adults, is primarily a slow-release formulation of melatonin appropriate for use in adults due to its size (round, with a diameter of 8 mm). Slenyto was approved for insomnia in children with ASD and Smith-Magenis syndrome in 2017, based on a 13-week placebo-controlled double-blind randomised study in children with ASD and neurogenetic disease using 1 mg mini-tablets of Melatonin-Neurim at the 2 mg and 5 mg doses. A significant increase in total sleep time (+32 min, p=0.034) and a shortened sleep latency (-25 min, p=0.011) as measured by sleep diary were seen

compared to placebo. The secondary endpoints Number of awakenings per night (p= 0.474) and Wake time after sleep onset (p=0.981) were not significantly affected.

3.2. Favourable effects

The primary evidence to support efficacy of Slenyto in the new indication including children with aged 2-18 years, is based on a sub-group analysis of the main clinical phase III study that was submitted to support the initial marketing authorisation approval of Slenyto (1 mg, 5 mg prolonged-release tablets) in children with ASD. In this clinical study, at baseline, 28.8% patients were diagnosed with ADHD before study initiation. Analyses showed similar responses between children with and without ADHD. Similar improvements in total sleep time (TST) were observed for patients with and without ADHD, with a treatment difference of 32.99 minutes [-22.52, 88.50]95% CI for patients with ADHD and 32.78 minutes [-3.14, 68.69]95% CI for those without ADHD. In addition, several published studies evaluated efficacy of melatonin (IR and PR) in children with sleep disorders and ADHD. Among these, three randomised placebo-controlled trials (RCTs) were conducted in children aged 6-12 years with ADHD demonstrating significant effects of IR melatonin on sleep latency in connection with insomnia. In addition, several published studies have summarised the results of the main clinical phase III study (NEU_CH_7911) with Slenyto. Taken together, literature data showed that Slenyto improved significantly sleep latency, total sleep time, sleep maintenance, daytime behaviour and quality of life in children with insomnia and ADHD, which in turn is supportive of the new indication.

Patients with neurodevelopment disorders including ADHD show significant clinical heterogeneity, where sleep disorders affect up to 70% of patients. The mode of action of PR melatonin on sleep disturbances is likely independent on the exact background of the neurodevelopmental disorder and patients with insomnia associated with altered diurnal melatonin secretion pattern and/or insufficient nighttime melatonin secretion should benefit from PR melatonin treatment. This notion is supported by the submitted studies showing consistent efficacy of melatonin products (IR and PR) on insomnia across various neurodevelopmental disorders including ADHD. Overall, the provided studies indicate that efficacy of PR melatonin is expected in children with ADHD and insomnia.

Based on differences in PK profile of PR melatonin vs. IR melatonin formulations, the MAH considers a potential benefit of Slenyto in the treatment of insomnia in children with ADHD given that Slenyto treatment would not only improve sleep-onset latency (as is the case for IR melatonin), but it also improves sleep maintenance and sleep duration. Total sleep time (TST) and sleep maintenance are the variables that are associated with daytime behaviour. In the Phase III clinical study NEU_CH_7911, there was a significant positive correlation observed between changes in TST and sleep maintenance, and the changes in total strength and difficulty questionnaire (SDQ) measuring behaviour and the clinical effects on total sleep time and maintenance were correlated with meaningful improvements in child behaviour and these improvements were correlated with parent/carer quality of life. Further, similar effects on sleep duration, latency and behaviour were seen on the subpopulation with hyperactivity and inattention at baseline (77% of the total population) as well as in 20 children aged < 6 years old with ADHD (albeit not statistically significant due to small sample size in this age group, the effect sizes were similar to the total population).

3.3. Uncertainties and limitations about favourable effects

To support claims of efficacy of PR melatonin (Slenyto) in the new therapeutic indication of treatment of insomnia in children and adolescents aged 2-18 with ADHD, where sleep hygiene measures have been insufficient, the MAH has provided a sub-group analysis of data from the previously submitted Phase 3

study NEU_CH_7911 combined with data from the literature and studies on off label use of PR melatonin in children with ADHD.

A subgroup analysis has generally several limitations and result of subgroup analyses is often viewed as exploratory and hypothesis-generating findings, rather than conclusive data. However, since the overall outcome of the main phase III study for both primary and secondary endpoints was positive, showing therapeutic benefits of Slenyto in treatment of insomnia in children with ASD with ADHD comorbidity, the performed subgroup analysis is considered acceptable.

Further, it is noted that the mean age of the children was approximately 9 years ± 4 years (mean ± SD) in the main phase III study (NEU_CH_7911), even if the inclusion criteria allowed subjects between 2 and 17 years to participate. Furthermore, due to small study size (n= 9-11 per group), the assessment of effect of PR melatonin on sleep parameters in the sub-population of children with ASD and ADHD comorbidity below 6 years of age in the phase III study is uncertain. However, the effect sizes in this age group were similar to the total population for all endpoints. Moreover, based on published efficacy data on IR melatonin in children with ADHD (e.g., van der Heijden et al., 2007), approved IR melatonin products (through WEU) include ADHD patients aged 6-17 years. In addition, a detailed assessment of an ADHD diagnosis is usually not performed in young children below 5-6 years of age. Overall, there are only limited data available to support efficacy of PR melatonin in children below 6 years of age. Therefore, the proposed age range including children from 2 to 18 years with ADHD was revised (e.g., children and adolescents aged 6 to 17 years).

Most literature studies on insomnia in children with ADHD are performed with IR melatonin (e.g., van der Heijden et al., 2007), which is a limitation since the applied PR melatonin formulation of Slenyto is different compared to IR melatonin products. Therefore, to support efficacy claims in the new indication, the MAH was asked to provide a justification with an in-depth discussion for extrapolation of efficacy data between IR melatonin and PR melatonin formulations. Following review of the Applicants response to the clinical efficacy MO, it appears reasonable to extend the indication of PR melatonin from the approved treatment of insomnia in ASD to treatment of insomnia in children with ADHD where sleep hygiene measures have been insufficient. However, the prosed indication wording as well as the suggested age range of children from 2-18 years with ADHD were revised.

3.4. Unfavourable effects

Safety for short-term unfavourable effects of melatonin is generally considered mild and well established.

Long-term safety data of Slenyto in children has been collected in the French RTU study, which was assessed in a previous procedure by the PRAC 2022 (EMEA/H/C/004425/REC/002.2).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In the present Type II variation, the MAH intends to add the new therapeutic indication of treatment of insomnia in children and adolescents aged 2-18 with Attention-Deficit Hyperactivity Disorder (ADHD), where sleep hygiene measures have been insufficient. ADHD is one of the most common psychiatric

diseases which affect children. Seventy percent of children with ADHD experience sleep problems and these patients have been shown to experience 30 to 60 minutes shorter sleep duration and have significantly more awakenings at night as compared to healthy children.

Supportive clinical efficacy data to support the new indication were presented from the previously submitted phase III clinical study (NEU-CH_7911). In children with sleep maintenance and/or onset insomnia and ADHD, PR melatonin improved average sleep duration and reduced sleep onset latency. In this study, children slept on average 57.50 minutes longer in the Slenyto-treated group (n=52), compared to 9.14 minutes in the placebo treated group and fell asleep on average 39.6 minutes faster in the Slenyto-treated group, compared to 12.51 minutes in the placebo treated group (n=48). Even if the effect sizes in the subgroup with ADHD are of a clinically relevant magnitude, the population is not completely representing the target population considering that the children were also diagnosed with ASD. Further, data with PR melatonin on off-label use in children with ADHD is not considered relevant evidence of efficacy. However, the MAH has also submitted literature data supporting an effect of melatonin on sleep disturbances in children with ADHD. In addition, a number of IR melatonin formulations have been approved in the EU/EEA through WEU applications to treat insomnia in children and adolescents aged 6-17 years with ADHD. Thus, there is external data with melatonin supporting the outcome of the main phase III study.

Most literature studies on insomnia in children with ADHD were performed with IR melatonin (e.g., van der Heijden et al., 2007), which is a limitation since the applied PR melatonin formulation of Slenyto is different compared to IR melatonin products. To further support efficacy claims in the new indication of ADHD, the MAH was asked to provide a careful justification with an in-depth discussion for extrapolation of efficacy data between IR melatonin and PR melatonin formulations and their discussion is considered sufficient. This issue was raised as a Major objection in the first round.

The proposed posology for the treatment of insomnia in children with ADHD include the maximum daily dose of 10 mg. Whilst no data on the 10 mg dose of PR melatonin has been presented in placebo-controlled studies in children with ADHD, the 10 mg dose is already approved for Slenyto. There are no safety issues observed in the patient population who received 10 mg dose in the clinical phase iii studies. The dosing of melatonin should generally start low and the lowest efficacious dose should be used, However, when clinically needed the 10 mg dose may be beneficial in certain patients with ADHD. Thus, in opinion of the Rapporteur, the inclusion of the maximum daily dose of 10 mg in the treatment of children with ADHD is acceptable.

3.6.2. Balance of benefits and risks

3.7. Conclusions

The overall B/R of Slenyto for treatment of insomnia in children with ADHD aged 6-17 years is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of insomnia in children and adolescents aged 6-17 with Attention-Deficit Hyperactivity Disorder (ADHD), where sleep hygiene measures have been insufficient, based on results from phase III study NEU_CH_7911 and literature. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the RMP has also been approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

4.1. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.