26 July 2018
EMA/556280/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Slenyto

International non-proprietary name: melatonin

Procedure No. EMEA/H/C/004425/0000

Note

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

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List of abbreviations

5GS	Standard categorical five-grade scale
6-SMT	6-sulphatoxymelatonin
AC	Active controlled
ACE	Angiotensin converting enzyme
ADHD	Attention deficit hyperactivity disorder
ADP	Adenosine diphosphate
AE	Adverse event
AFS	Awaking from sleep
ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ASAT	Aspartate aminotransferase
ASD	Autistic Spectrum Disorders
AUA	American Urology Association
AUC_{0-24}	Area under the curve from 0 to 24 hours
BFW	Behaviour following waking
BMI	Body mass index
BP	Blood pressure
BPH	Benign prostatic hyperplasia
CFU	Colony Forming Units
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression of Improvement
CHESS	Check-list Evaluation of Somatic Symptoms
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
C_{max}	Peak plasma concentration
CNS	Central nervous system

CO	Crossover
CPMP	Committee for Proprietary Medicinal Products
CR	Controlled release
CRF	Case report form
CSDI	Composite Sleep Disturbance Index
DB	Double-blind
DHT	Dihydrotestosterone
DR	Dose-ranging
DSC	Differential Scanning Calorimetry
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
DSPS	Delayed sleep phase syndrome
DWAPSO	Duration of wakenings prior to sleep
EC	European Commission
ECG	Electrocardiogram
EEG	Electroencephalographic
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	Full analysis set
FR	Fast release
GC	Gas Chromatography
GCP	Good Clinical Practice
GI	Gastrointestinal
GTS	Getting to sleep
HbA1c	Glycosylated haemoglobin
HDPE	High Density Polyethylene
HPA/HPG	Hypothalamo-pituitary-gonadal-adrenal
HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
ICD-10	International Classification of Diseases 10th Revision
ICH	International Council for Harmonisation

ICP OES	Inductively Coupled Plasma Optical Emission Spectrometry
ICSD	International Classification of Sleep Disorders
IPC	In-process control
IR	Infrared
ITT	Intent-to-treat
KF	Karl Fischer
LDL	Low density lipoprotein
LSEQ	Leeds Sleep Evaluation Questionnaire
MAP	Mean arterial pressure
MC	Multi-centre
MCHC	Mean corpuscular haemoglobin concentration
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed-effects model for repeated-measures
MRT	Motor reaction time
MT	Movement time
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NNT	Number needed to treat
NSAIDs	Non-steroidal anti-inflammatory drugs
PACMP	Post Approval Change Management Protocol
PC	Placebo-controlled
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PP	Per-protocol
PSA	Prostate specific antigen
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSUR	Periodic safety update reports
PUMA	Paediatric-use marketing authorisation

PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QOD	Quality of day
QON	Quality of night
QOS	Quality of sleep
QP	Qualified person
QSAR	Quantitative Structure-Activity Relationship
R	Randomised
REM	Rapid eye movement
RH	Relative Humidity
RSD	Relative standard deviation
RSL	REM sleep latency
SAE	Serious adverse event
SAP	Statistical analysis plan
SB	Single blind
SC	Single centre
SD	Standard deviation
SDQ	Strength and Difficulties Questionnaire
SED	Standard error of differences
SEF	Sleep efficiency
SL	Sleep latency
SmPC	Summary of Product Characteristics
STSH	Stage shifts
SWS	Slow wave sleep
TAMC	Total Aerobic Microbial Count
TEA	Test of Everyday Attention
TRT	Total reaction time
TRUS	Trans-rectal ultrasound
TSA	Time spent asleep
TSE	Transmissible Spongiform Encephalopathy
TSH	Thyroid stimulating hormone

TST	Total sleep time
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
WAPSO	Wakenings prior to sleep onset
WASO	Wakenings after sleep onset
WHO	World Health Organisation
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant RAD Neurim Pharmaceuticals EEC Ltd. submitted on 3 January 2017 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Slenyto, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 April 2016.

The applicant applied for the following indication:

Treatment of insomnia characterized by maintenance problems and/or sleep onset difficulties in children aged 2-18 with Autism Spectrum Disorders (pervasive developmental disorders) and neurogenetic diseases.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0148/2016 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/0148/2016.

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 applicant 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.

New active Substance status

The applicant indicated the active substance melatonin contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant 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 Boran

The application was received by the EMA on	3 January 2017
The procedure started on	18 May 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 August 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	4 August 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 August 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	04 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 July 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Slenyto on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The disease state is twofold; first, it consists of a specific variant of (chronic) insomnia characterized by maintenance problems or sleep onset difficulties and second, this insomnia should occur in children with Autism Spectrum Disorders (pervasive developmental disorders) and neurogenetic diseases.

2.1.2. Epidemiology

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.

In children with neurodevelopmental or psychiatric comorbidities it is as high as 50–75%. This group of children is composed of many subpopulations with varying degrees of impairment and symptomatology, including pervasive developmental disorders ([PDDs] autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and PDD not otherwise specified); ADHD; genetic disorders, such as Angelman syndrome; and chronic neurologic disorders, such as epilepsy and Tourette's disorder. 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, characterised by difficulties initiating or staying asleep, and usually far more difficult to treat than their normally developing peers.

2.1.3. Aetiology and pathogenesis of sleep disturbance in children with ASD and neurogenetic disease

Children with neurodevelopmental disorders might suffer from low endogenous melatonin secretion and abnormal circadian rhythmicity (Melke et al, 2008; Richdale 1999; Tordjman et al, 2005). Lower melatonin concentrations have been found in blood and urine samples from children with autism which might explain the abnormal development of sleep/wake cycles, noted since the first year of life (Phillips and Appleton, 2004). In cases of Smith-Magenis syndrome (SMS), a genetic disorder involving mental retardation and extremely severe sleep disorder, patients manifest a severe phase shift of their circadian melatonin rhythm with the diurnal secretion of this hormone (De Leersnyder et al, 2003; De Leersnyder et al, 2011). Melatonin assists the thalamus in opening the 'sleep gate' for non-rapid eye movements (NREMs) and promotes spindle formation. Thus, melatonin has a modulatory influence on sleep onset and maintenance.

2.1.4. Management

Currently there are no approved medicinal products indicated for hypnotic use in the paediatric population. This results in physicians prescribing drugs without a proven record of safety and efficacy in children, or a determination of paediatric dosing. Nevertheless, the lack of appropriately labelled drugs is not reflected in the everyday situation of current use. Results of three surveys and a retrospective chart review showed that paediatricians 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, off-label Circadin or IR melatonin prescribed on a special permission basis, antipsychotics,

benzodiazapines, 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 hyperarousal.

2.2. About the product

This application is for Slenyto prolonged-release tablets containing 1 or 5 mg melatonin as the active substance, formulated as film-coated, prolonged-release tablet, age appropriate oral solid dosage form (tablet). The active substance, melatonin, is a hormone secreted by the pineal gland. Melatonin is involved in several physiological processes (some of which appear to be species-specific) in animals and humans:
1. The primary effects lie in the central nervous system (CNS), where melatonin modulates synchronisation of the biological clock and promotes sleep. This appears to result from melatonin’s stabilising and phase-shifting effects on the suprachiasmatic (SCN) of the hypothalamus and the sleepinducing effect during the daytime.
2. The hypothalamus-pituitary-gonadal axis, by which melatonin modulates seasonal reproduction and pubertal development, especially in seasonal breeding animals.
3. The peripheral organs, by which melatonin supports the immune system and appears to inhibit growth in some tumours (Arendt, 1988), slowing of ageing and amelioration of depression and a wide range of metabolic/physiological disorders.

2.3. The development programme/Compliance with CHMP Guidance/Scientific advice

The following studies were conducted under the PIP:

1. An open label, GCP Single Ascending Dose, Cross-over Study to Assess the Pharmacokinetics of Circadin (Prolonged-Release Melatonin) tablets in Children with Neurodevelopmental disorders and Sleep Disturbances.

2. A pivotal GCP double blind placebo controlled study was performed A Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Circadin to Alleviate Sleep Disturbances in Children with Neurodevelopmental Disabilities aimed to assess efficacy and safety after 3 months double blind period and additional 3 months open label period (6 months in total) of Slenyto 1 and 5 mg tablets.

Regulatory information on the PIP

Under Article 13 of Regulation (EC) No 1901/2006, a PIP was proposed for the treatment of insomnia characterised by maintenance problems and sleep onset difficulties in children with pervasive developmental disorders, also called Autistic Spectrum Disorders (Autistic Disorder, Rett’s disorder, Asperger’s Disorder – DSM-IV 299.0, 299.10, 299.80) and neurogenetic diseases (Smith Magenis syndrome, Angelman syndrome, Bourneville’s disease) aged 2-18 years. A waiver has been requested for 0-2 years on the grounds of lack of significant therapeutic benefit and approved by the PDCO.

2.4. General comments on compliance with GMP, GLP, GCP

Clinical studies supporting this MAA were performed in Europe and Israel and in compliance with Good Clinical Practice (GCP) as per the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline.

All pivotal company sponsored toxicity studies i.e. combined repeat dose toxicity/oncogenicity study in the rat, a full battery of genotoxicity studies, a fertility and early embryonic development study and pre-and post-natal study in the rat, an embryo-foetal developmental study in the rabbit, juvenile toxicity in the rat and a carcinogenicity assessment in transgenic rasH2 mice were conducted in compliance with GLP. Toxicity to

reproduction was assessed according to International Conference of Harmonisation (ICH) Guidelines for the Detection of Toxicity to Reproduction (June 1993).

Although the GLP status of the literature data provided cannot be verified some results show good consistency and are published in peer-reviewed journals, hence scientific integrity can be assumed.

2.5. Type of application and other comments on the submitted dossier

Legal basis: Full application according to Article 8(3) of Directive 2001/83/EC, known active substance.

Article 30 (Paediatric use marketing authorisation - PUMA) of the Paediatric Regulation (EC) No 1901/2006 applies to this application.

2.6. Quality aspects

2.6.1. Introduction

The finished product is presented as prolonged-release tablets containing 1 or 5 mg of Melatonin as active substance.

Other ingredients are:

For the 1 mg tablet core: ammonio methacrylate copolymertype B, calcium hydrogen phosphate dihydrate, lactose monohydrate, colloidal anhydrous silica and talc, magnesium stearate

For 1 mg tablet film coating: carmellose sodium (E466), maltodextrin, glucose monohydrate, lecithin (E322), titanium dioxide (E171), iron oxide yellow (E172) and iron oxide red (E172).

For the 5 mg tablet core: ammonio methacrylate copolymer type A, calcium hydrogen phosphate dihydrate, lactose monohydrate, colloidal anhydrous silica and magnesium stearate

For the 5 mg tablet film coating: carmellose sodium (E466), maltodextrin, glucose monohydrate, lecithin (E322), titanium dioxide (E171) and iron oxide yellow (E172).

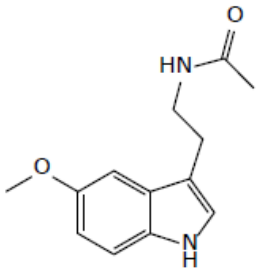
The product is available in PVC/PVDC opaque blisters with aluminium foil backing and HDPE bottles closed with induction sealed polypropylene caps, as described in section 6.5 of the SmPC.

2.6.2. Active Substance

General information

Melatonin is a known active substance. The chemical name of melatonin is *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl] corresponding to the molecular formula $C_{13}H_{16}N_2O_2$. It has a relative molecular mass of 232.27 g/mol and the following structure (Figure 1):

Figure 1: active substance structure



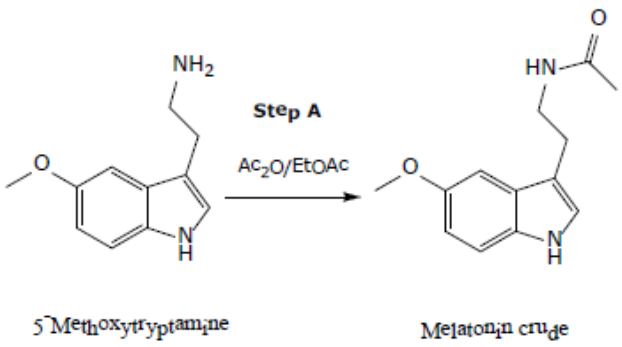
The chemical structure of melatonin was elucidated elemental analysis, nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C), mass spectrometry, UV/Vis spectroscopy, infrared spectroscopy and X-ray crystallography. The particle size of the active substance was measured by laser counting method.

Melatonin appears as a slightly white to off-white, odourless, crystalline, non-hygroscopic powder. Sufficient information on the solubility in organic solvents has been provided. Melatonin has limited aqueous solubility. Melatonin does not contain any chiral centres. Polymorphism has not been observed through XRPD analysis. The drug product is not photosensitive.

Manufacture, characterisation and process controls

Melatonin is currently synthesized in one main step using starting materials with acceptable specifications. The step of the synthesis leading to active substance is described below (**Figure 2**).

Figure 2: active substance manufacturing process



Manufacturing, testing and release of melatonin is carried out at one site, while micronisation and testing of particle size is done in a separate site.

A major objection was raised requesting re-definition of the starting material as an intermediate as a one-step synthesis is not aligned with the current recommendations for manufacture of active substances as described in ICH Q11. CHMP judged that not enough of the process was included in the dossier to be able to fully understand the origin, fate and purge of impurities or to mitigate risks associated with contamination from non-GMP synthesis and changes to the synthetic process of 5-methoxytryptamine. The applicant was requested provided detailed information on the manufacturing process before the last step All synthesis steps have been described from simple starting materials where all reagents, catalysts and solvents and reaction conditions were indicated for each step. It was not possible during the procedure to find a manufacturer who could conduct all these steps under GMP. However, it is considered that there is no immediate risk to active substance quality. However, re-definition will help ensure the quality of the active substance throughout the life-cycle of the product.

In order to address CHMP's concern, the applicant presented a post approval change management protocol (PACMP), where two options for finding an approvable GMP-compliant manufacture of the active substance were proposed. The carry-over of reactants, solvents, catalysts, intermediates and related substances has been described. The PACMP contained detailed descriptions of the changes and the timelines to implement them, a risk assessment of the impact of the changes on product quality, discussion on the control strategy, description of the studies to be performed, and a plan for stability studies. This was deemed acceptable by CHMP.

The information provided on the characterisation of the active substance is considered acceptable. Sufficient information on carry-over of impurities to the current starting material and active substance was provided. Melatonin is a known active substance with a known impurity profile and low degradation.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials and reagents have been presented. Impurities arising from the starting materials and intermediates, degradation products, residual solvents and elemental impurities were discussed in detail. The applicant presented an assessment of genotoxic impurities that lists the potential impurities that would need to be controlled to the TTC limit and concludes that they are all controlled to below the TTC by the purge factors. All other structures can be treated as non-mutagenic and ICH Q3 thresholds can be applied. For this, an *in silico* evaluation of the intermediates and known impurities was performed, using a rule-based program (ToxTree) and a QSAR model (T.E.S.T.). For structures with *in vitro* data (e.g. Ames test), no *in silico* evaluation was performed. Potential and actual impurities were well discussed with regards to their origin and characterised.

Melatonin is packaged after manufacture in HDPE drums with polythene bag liners. The polyethylene bags are of low-density polyethylene, natural coloured. The material complies with Ph. Eur. 3.1.3 and the bags are produced according to GMP for articles intended for food contact according to EC 2002/72/EC and EC 10/2011 as amended. No phthalates and other additives are used in the manufacture of the polyethylene bags.

Specification

The active substance specification includes tests for appearance, identity (IR, UV, melting point, HPLC), assay (HPLC), purity (HPLC), impurities (HPLC), residual solvents (GC), water content (Ph. Eur. - KF), heavy metals (Ph. Eur. – ICP OES), residue on ignition (Ph. Eur.), microbial quality (Ph. Eur) and particle size distribution (Ph. Eur. - laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph for IR, UV, water content, melting point, microbiological purity and heavy metals.

Batch analysis data from 15 production scale lots (30 to 55Kg scale) of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three full scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH), for up to 60 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, identity, related substances, assay, water content, microbial quality and particle size. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No out of specification have been identified during the accelerated (6 months) and long-term stability up to 60 months. No degradation or other negative trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Melatonin was found to be chemically stable under the conditions of the study but irradiated samples showed some discolouration. A thin top layer became brown but the main quantity remained white and the NMR and HPLC results did not indicate any significant decomposition. Based on these results storage conditions “Store below 25 °C, protected from light” are proposed.

Results under stressed conditions (1 day at 70 °C, 1 day at 70 °C in water / methanol (1:1), 1 day at 70 °C in 0.1 N HCl / methanol (1:1), 1 day at 70 °C 0.1 N NaOH, methanol (1:1), 1 day ambient in 10% H_2O_2 / methanol (1:1), 1 day irradiation with UV light) were also provided on one batch. Degradation products were identified and quantified by HPLC. Samples were stable after1 day at 70 °C and after 1 day irradiated with UV light. Samples degraded, mainly by hydrolysis under the other stressed conditions except for under oxidative conditions where different degradation pathways were observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 5 years when stored in the proposed pack at temperatures below 25 °C.

2.6.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The drug product is supplied as round 3 mm diameter bi-convex tablets. The tablets are film coated and the two different strengths of 1 and 5 mg are differentiated by the colour, pink and yellow respectively. The size of the tablets is considered appropriate for paediatric patients. The tablets are intended for prolonged release of the active substance. Hydrophobic polymers included within the matrix formulation offer greater control of drug release. Ammonio methacrylate copolymers are insoluble but exhibit pH-independent swelling in all parts of the GI tract. They are non-biodegradable, non-absorbable and non-toxic.

All the excipients used in the formulation of the 1 mg and 5 mg paediatric core tablets are the same as currently used in the 2 mg melatonin tablet marketed by the applicant as Circadin, although they are used at different ratios. However, the copolymer type B that is used in the 1 mg tablet is changed to copolymer type A for the 5

mg tablet and the glidant, talc, is removed All core tablet excipients are standard pharmaceutical tablet ingredients and are used for their standard function and at standard concentrations for pharmaceutical tablet formulations. The 1 mg and 5 mg paediatric tablets are film coated using standard ingredients for coating formulations and all components are also used for their standard function and at standard concentrations in film-coating.

The starting point for the 1mg and 5 mg tablet product formulations development was the already marketed prolonged-release product Circadin (same active substance, 2 mg tablets) and the aim was to maintain similar prolonged-release characteristics for the new formulations which would have higher surface area-to-volume ratios. The formulation for the 1 mg tablet cores uses the same ingredients as Circadin while the 5 mg tablet uses the same ingredients as Circadin except for the release-controlling ingredient ammonio methacrylate copolymer where type A is used instead of type B and the removal of the talc. However in both cases, due to their small size, the 1 and 5 mg tablet cores have a much higher concentration of active ingredient than for Circadin in order to keep the tablets small and therefore age-appropriate.

The coated tablets are not designed to be chewed because of the prolonged release nature of the product. The coating formulations do not contain sucrose but do contain dextrose and maltodextrin as part of the commercial formulation. These help the coatings to taste acceptable to the patient and so assist with patient compliance. The tablets were especially developed for the paediatric population, being 3 mm in diameter (one third that of the Circadin tablet). This makes them easy to swallow but difficult to chew. The tablets can be put into food like yogurt, orange juice or ice-cream to facilitate swallowing and improve compliance. Since the target population is very sensitive to taste and smell, the tablets had to be coated to mask taste and odour properties and aid swallowing. Finally, the coating protects the active substance from changing colour on exposure to light.

Strategies for differentiation such as the use of embossing are not feasible for such a small tablet and target population. Markings would be very small and hard to distinguish. Different shapes, for example round versus oval, also might not be obvious at this small size and difficult to swallow. More extreme changes in shape such as to a pentagonal tablet have adverse considerations for tooling, in-use lifetimes and ease of manufacture. Furthermore, a change in the developed shape is expected to critically affect the prolonged release dissolution profile and *in vivo* pharmacokinetic profile, which are of utmost importance to achieve the efficacy desired in improving sleep maintenance throughout the night. For these reasons, a difference in colour was felt to be the most effective and feasible option. Two different colours would differentiate between the strengths and prevent errors in dosing.

Initial development used film-coats with azo-dyes which are contraindicated in paediatric patients due to potential allergic reactions. Therefore, the colouring agents were changed to iron oxides as these are more acceptable alternatives. A major objection was raised at the beginning of the assessment and the applicant replaced the azo-dye with iron oxide during the procedure. Attempts were made to choose the closest colour (yellow) to the orange colour used in the clinical studies. For the products with the new colours, there is no change in the formulation of the tablet cores and it has been validated that the change in colourants had no effect on the specificity of analytical test methods.

The formulation development was based on the already marketed 2 mg tablet (Circadin) but using a simplified manufacturing processes. Several formulations of the 1 mg tablet were evaluated and compared with dissolution profile of the commercial 2 mg Circadin tablet before the final composition of the 1 mg tablet was decided.

The 1 mg tablet was developed first and the 5 mg tablet was developed later, trying to get the same release profile as the 1 mg tablet. Several prototype formulations were produced in order to get the preferred 5 mg

tablet formulation. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. There are no overages in the 1 mg and 5 mg paediatric tablets cores.

The formulation proposed for the commercial product, apart from the colorant, was used in the pediatric PK study and the main pediatric study and these studies therefore used product representative of the commercial product.

A dissolution study comparing the release rates of the 1 mg tablet and the 5 mg tablet was carried out at the tablet manufacturing site. The studies were carried out at pHs of 1.2, 4.5 and 6.8. The applicant provided further calculations of similarity factors to present the comparison of the dissolution profiles more clearly. The applicant justified the chosen dissolution method. The results demonstrate that the dissolution method is capable of discriminating between the different formulations and manufacturing processes. Data for some batches being non-acceptable was presented showing the discriminatory capacity of the method. Also the limits were tightened to increase the discriminatory potential of the method. The results also demonstrate that the new colouring agent does not influence the *in vitro* dissolution profile.

The primary packaging is PVC/PVdC/Aluminium blister packs and HDPE bottles with polypropylene caps. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The bottle pack uses a child resistant tamper-evident screw cap and the blister packs are single dose units and therefore mitigate against over-dosage. This should ensure that the younger of the patients do not encounter any greater risk of overdose than for other pediatric presentations.

Manufacture of the product and process controls

Two different manufacturing processes are proposed for the two tablet strengths The manufacturing process consists of 7 main steps. The processes are considered to be non-standard manufacturing processes. The 1 mg tablets are prepared by dry mixing, direct compression of tablet cores followed by coating and packaging. The 5 mg tablets are manufactured by dry mixing , dry slugging , milling, compression and finally coating and packaging. Tablet cores are manufactured and coated at different sites.

Process validation studies have been carried out for the manufacture of the tablet cores, the film-coating of the cores at and the blister packing of the film coated tablets at each respective site. Initially, the applicant did not provide any process validation data and this was raised as a major objection as the manufacture of modified release products is considered a non-standard process. Batch analysis data for 3 production scale batches of each strength was presented by the applicant and found to be acceptable. All batches complied with the proposed specification.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise tests for description, identification (HPLC), assay (HPLC), related substances (HPLC), water content (Ph. Eur. - KF), uniformity of dosage units (Ph. Eur.), dissolution (- Ph. Eur.) and microbial limit testing (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 batches of each strength at full scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Initially, the applicant only submitted stability data (long-term, intermediate and accelerated) from 1 production scale batch, the rest being from smaller than pilot scale batches. According to ICH Q1A data from stability studies should be provided on at least three primary batches of the drug product. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified. This issue was raised as a major objection. Also, only data on the 1 mg tablets was available. Therefore, another major objection was raised requesting stability data from the 5mg tablets, especially as the formulations and manufacturing methods are different. Further batch data analysis was made available during the procedure that resolved both major objections and supported the current shelf-life claim for both strengths and primary packages.

After the company was requested to remove the azo-dye contained in the coating, new batches of both 1 and 5 mg were manufactured with the iron oxide colorant and new stability studies were initiated.

At the time of the opinion, for both tablet strengths, stability data from three commercial scale batches of finished product (with the new film coating) stored for up to three months under long term (25 ºC / 60% RH), intermediate conditions (30 °C / 65% RH) and under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The difference in coating is not seen as a major concern and the commercial scale batches manufactured by the proposed manufacturer with the azo-dye-based coating can be seen as supporting stability studies in combination with the new study with the iron-oxide-based coating. The stability data from the 1 mg tablet batches cannot been seen as supportive for the 5 mg since they are manufactured with another process and with a different qualitative composition.

Samples were tested for appearance, assay, impurities, water, dissolution and microbial contamination with the same limits as the release specifications. The analytical procedures used are stability indicating. No significant changes have been observed on the newly coated tablets. The supportive batches showed good stability for assay, while the number of detectable impurities increases during storage, the total impurity content remains very low compared to the proposed limit of NMT 1.0%. Water content, dissolution and microbial limit test show no discernible trends in either pack. Observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Active substances and Products.

Based on available stability data, the proposed shelf-lives of 36 months when stored at temperatures up to 30 °C for the 1 mg tablet and 15 months for the 5 mg tablet with a label statement of “do not store above 30 °C” stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

According to the certificate of analysis from the supplier of magnesium stearate, the material is derived from edible non-animal sources.

There are no other excipients derived from animal or human origin.

2.6.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

This product was developed as a PUMA following an agreed paediatric investigation plan (PIP). The finished product, an age appropriate dosage form, is designed for prolonged delivery of melatonin using a polymeric matrix tablet. The modified release profile maintains melatonin levels during sleep. The dimensions of the bi-convex 3 mm tablets make them easy to swallow.

Major objections related to the use of azo-dye on the coating, dissolution method, process validation, batch data and shelf life, were resolved during the assessment. Particularly, the issue with starting materials major objection has been satisfactorily addressed through the implementation of a PACMP.

2.6.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.6.6. Recommendation(s) for future quality development

Not applicable.

2.7. Non-clinical aspects

The main part of the non-clinical data provided by the Applicant was identical to the non-clinical dossier which has already been assessed in connection to the Circadin procedure (EMEA/H/C/695). In support of the present PUMA application, the Applicant conducted two juvenile toxicity studies with melatonin in rats, which will be assessed in relation to the non-clinical data previously provided for Circadin.

2.7.1. Pharmacology

Primary pharmacodynamics

The current understanding of endogenous melatonin is substantial, especially regarding melatonin's involvement in the circadian timing system, but the putative role that endogenous melatonin may play in regulating sleep and how this role is mediated remains unclear. Sleep is a difficult area to investigate and no simple animal models are available. In particular, there is no acceptable animal model for investigating the sleep modulating effects of melatonin, since melatonin induces changes that are typical for the dark period for each species, namely waking in nocturnal rodents and sleepiness in the diurnal human. The only effect which can be assessed in this respect is the sedative hypnotic activity as determined by the potentiation of barbiturate-induced sleep in rodents. In this context, the Applicant has conducted two studies to investigate the primary pharmacodynamic profile of melatonin which showed (i) that orally administered melatonin can abolish benzodiazepine-mediated suppression of brain melatonin binding sites, suggesting that benzodiazepine-mediated suppression of brain melatonin binding sites can be abolished by melatonin administration and (ii) that intraperitone-ally administered melatonin affected hexobarbital hypnotic onset time (20mg/kg) and hexobarbital-induced sleeping time (100mg/kg).

Secondary pharmacodynamics

Apart from being involved in the sleep regulation, melatonin is also associated with many other physiological processes. These processes, which are considered secondary to sleep regulation, include photoperiodism, endocrine regulation of sexual function in some animal species, immune-augmenta-tion and free radical scavenging and antioxidant properties. Melatonin has been shown to regulate pubertal development in some juvenile mammals, but no such effect was observed in the toxicology studies in adult and /or juvenile rats. Also, there is no clinical data so far supporting the risk of hormonal disturbances or effects on pubertal development by melatonin treatment even though long-term studies are still warranted (see Clinical Safety part of this report). Effects by melatonin on photoperiodism and endocrine function has mainly been reported in seasonal breeding species and related to route and time of administration rather than dose-dependency. Melatonin has demonstrated anti-carcinogenic and gastrointestinal protective effects due to its free radical scavenging capacity. Many of the observed effects by melatonin have been species-specific or are manifested at doses far in excess of those proposed indication and therefore considered to be of low clinical significance. The claims of effects by melatonin on ageing and the immune system are general indications of possible biological activities that still require critical exploration.

Safety Pharmacology

Central Nervous system

In mice, the Irwin test showed that at doses >8mg/kg melatonin had no behavioural effects. At

16 mg/kg a slight sedation was observed. Such sedation was also reported in the repeated dose studies conducted by the Applicant in rats. At doses of 64, 128 and 256 mg/kg decreased fear, reactivity, muscle tone and hypothermia were observed with dose-dependent intensity and duration. At 128 mg/kg it also showed analgesic activity in the four-plate test (Guardiola-Lemaitre et al., 1992,Pharmacology Biochemistry and Behaviour, 41, 405). Daily administration of 2.5-10mg/kg melatonin prior to the swimming test significantly reversed the increased immobility period that was observed on chronic exposure to swimming test. This effect was reported to be comparable with that of GABA-benzodiazepine (BZ) receptor agonists, appearing to involve

GABA-benzodiazepine receptors (Raghavendra et al., Eur. Neuropsychopharmacol.10(6):473). In other studies, acute administration of melatonin did not reveal antidepressant activity. In the juvenile toxicity studies performed in rats, no effects of on central nervous system (functional observation battery) were observed at ≥80 mg melatonin/kg/day by the oral route.

Endocrine and reproductive systems

Melatonin regulates pubertal development in some juvenile mammals. In seasonal breeders, melatonin seems to act as either pro-gonadotrophic or as anti-gonadotrophic according to the period of the year (autumn-winter/short days or spring-summer/long days respectively. Melatonin has also been shown to influence secretion of several hormones (luteinizing hormone (LH) and prolactin, corticosteroids, thyroid hormones and insulin) in animals and in humans in some situations. In rats administered 0.1 mg/kg melatonin s.c. for 4 weeks, Olivares et al.(1989) Arch. Biol. Med. Exp., 22, 378, observed abnormal progression of spermatogenesis coupled to a decreased production of testosterone by Leydig cells, which were considered as secondary to a decrease in LH hormone production resulting in an impairment of the Leydig cell function. In female rats Liu and Meites (1973) Endocrinology, 93, 152, observed that a single intravenous dose of melatonin increased serum prolactin levels. In Syrian hamsters several authors observed either decrease or an increase of the prolactin, follicle stimulating hormone and LH hormones. It is possible that the conditions of administration such as the period of the year or the time of the day, the duration of the administration period may have influenced the results. In hamsters, endogenous and cyclically administered melatonin (0.0025-0.025 µg) depressed the thyroid function. Melatonin given to blinded hamsters for 10 weeks in the drinking water partially restored thyroxin levels and testis weights normally associated with blinding. In the juvenile toxicity studies performed in rats, no effects of on endocrine and reproductive systems (estrous cyclicity, vaginal opening, preputial separation and sperm quality) were observed at ≥80 mg melatonin/kg/day by the oral route.

Cardiovascular and respiratory systems

Melatonin receptors were identified on the anterior cerebral and caudal arteries of rats and on the coronary and pulmonary arteries of pigs. In rats, a dose-related fall of mean arterial pressure, heart rate and also of brain serotonin release were observed in consequence of 30-60 mg/kg melatonin i.v. Bradycardia was abolished by pre-treatment with bilateral vagotomy thus suggesting that it may be mediated through a parasympathetic action. (Chuang et al.,1993, Pharmacology, 47, 91). Also studies in porcine and coronary arteries suggest the potential for melatonin to have tensive effects (Viswanathan et al., 1992 Neuroendocrinology, 56, 864; Weekley, 1993, Pulmonary Pharmacol., 6, 149). In baboons, 0.3 to 0.4 mg/kg melatonin, i.v. caused a statistically significant increase of the cardiac output and ventricular ejection associated to a reduction in heart rate (Bosman et al., 1991, J. Pineal Res.24, 62). The Applicant has submitted an evaluation of the cardiovascular and respiratory effects in rats. At a dose of 100 mg/kg a slight decrease of heart rate and blood pressure were observed. The Q-T interval of the ECG and the respiratory rate were not changed. Also in humans the evaluation of ECG was performed and reported as not presenting any effects on the Q-T interval.

Pharmacodynamic drug interactions

In the literature review provided, the secretion of melatonin has been shown to be affected by adrenergic agonists and antagonists, antidepressants, opiate agonists and antagonists, prostaglandin synthesis inhibitors, benzodiazepines, barbiturates and glucocorticoides. In humans, co-administration of Circadin with thioridazine,

imipramine and zolpidem showed pharmacodynamic interaction (increased sedation), with no pharmacokinetic interaction, while coadministration with cimetidine had no pharmacodynamic interaction but increased plasma melatonin concentration. This is reflected in the SPC section 4.5.

2.7.2. Pharmacokinetics

Pharmacokinetic studies of exogenous melatonin in animals are available in the literature. The Applicant has conducted toxicity studies in the rats, dogs, and rabbits from which toxicokinetic data were obtained.

Absorption and bioavailability

In the study of Yeleswaram et al (1997) the pharmacokinetics and bioavailability of melatonin was investigated in rats, dogs and monkeys after intravenous and oral administration. The mean oral bioavailability of 10 mg/kg of melatonin was 53.5% in rats and >100% in dogs and monkeys. The low bioavailability (16.9%) in low doses (1mg/kg) in dogs suggests non-linear pharmacokinetics in experimental animals and also in humans, probably as a result of first-pass metabolism in the liver.

Distribution

Melatonin seems to distribute fast through tissues and even after brain injection is was shown, in rats, to clear after 5 minutes. The steady state distribution volumes in animals range between 1.05 and 1.48 L/kg, with a typical value of 0.55 l/kg in man at doses of 5-10 and 0.08-0.15 µg/kg, respectively.

Literature data show that in rat and humans most circulating melatonin is bound to albumin. Melatonin seems also bind to haemoglobin and calmodulin.

Metabolism

According to available data, melatonin appears to be mainly metabolised by CYP1A1 and CYP1A2. From the chromatographic analysis of urinary metabolites obtained in rats administered intravenously with labelled melatonin three peaks were identified, two of them corresponded to the glucoronic and sulphate conjugates of 6-hydroximelatonin and the third compound was not completely characterised.

The major metabolite accounting for 70%-80% of the radioactivity was the sulphate conjugate of 6-hydroxymelatonin whereas the glucoronic acid conjugate represented 5%. The unidentified metabolite corresponded to 12% of radioactivity. *In vitro* metabolism studies using liver microsomes also indicates that 6-hydroxylation is the major route. Also 5-methoxyindoleacetic acid appears to be formed by deacetylation of melatonin followed by deamination.

Elimination and excretion

The main excretion route of the melatonin metabolites is renal. In rats administered intravenously with labelled melatonin, after a 48 hour collection of urine and faeces, the total amount of radioactivity in urine was 60%-70% of the administered melatonin and about 15% was found in faeces.

2.7.3. Toxicology

Single-dose toxicity

Data from literature points towards a low acute toxicological profile by the oral route. The main effects observed at high doses were sedation, lethargy, and vasodilatation. Even higher doses led to impairment of righting, placing and flexor reflexes, marked reduction in body temperature and respiratory distress preceding death. In context of the proposed human dose of 5 mg melatonin (maximum 0.42 mg/kg), these effects are not expected to occur and not clinically relevant.

Repeat-dose toxicity

Rats

The toxicological profile of melatonin after a 90-day period of administration was low but very low doses were used in the study (0.3, 1.2 and 6 mg/kg/day). The toxicokinetic data from the study showed mean plasma concentrations up to 50 pg/ml, which are lower than those expected to be reached in humans, but the time of sampling is not specified. A decreased body weight gain of the animals at 1.2 mg/kg/day (males) and 6.0 mg/kg/day) (males and females). Also decreased testis and increased kidney relative weights were observed at 6 mg/kg/day.

A combined 13-week study in rat with a 4-week recovery period coupled to a 26-week toxicity and a 104-weeks carcinogenicity phase was submitted in the dossier. The oral dose levels used in this study were 0, 15, 75 and 150 mg/kg/day.

In the 13-weeks and the 26 weeks studies increased haemoglobin concentration and platelet counts were observed at 75 and 150 mg/kg/day treated animals. Increased liver weights with minor centrilobular hepatocytic hypertrophy were observed. Increased testes, prostate and epididymides weights were seen in males administered 75 and 150 mg/kg/day. At 26 weeks, macroscopically dark thyroid was also recorded in several animals dosed 150 mg/kg/day. Microscopically, minor liver hypertrophy was seen in some high dose animals but reported as less obvious than in the 13 weeks treated group. Toxicokinetics showed that melatonin was systemically absorbed at all dose levels of melatonin at the 13, 26 and 104 week time-points in both sexes. In general, when comparing data from day 1 and 7, the C_{max} values of the females were higher than those of the males and the maximum concentration was achieved over a longer period of time. There appeared to be a sex difference in increase of AUC values compared to the increase in dose received. All values were reduced upon repeated exposure of melatonin suggesting reduced absorption, increased elimination or induction of enzymes. From data obtained for the complete period - between day 1 and week 104, there was no apparent sex difference observed and there was no accumulation of melatonin over the full dosing period. In the repeat-dose toxicity studies in rats the plasma concentrations measured along the study decreased along the exposure time. No further AUC values were determined. The systemic exposures in rats along the study are therefore not evaluable and appropriate animal to human exposure ratios cannot be calculated. The AUC_{0-24h} after 2 mg melatonin in human adults is 3846 pg.h/ml.

Dogs

In a 6 month repeat-dose toxicity study in dogs AUC and C_{max} increased with dose in an unproportional manner indicating saturable kinetics. There was no relevant time or sex difference in dogs. Increased serum glucose

levels were observed at some time points of the study. Microscopic examination revealed pituitary gland and parathyroid cysts, adenomyosis of the uterus, capsular fibrosiderosis of the spleen and cytoplasmatic rarefaction of hepatocytes consistent with the presence of glycogen. Based on toxicokinetic data the C_{max} values obtained with the doses 1.5 and 8.0 mg/kg/day were high in excess to the predicted clinical exposure.

Genotoxicity

A full battery of genotoxicity tests according to ICH standard have been performed. The Ames test, *in vitro* gene mutations in mouse lymphoma cells*, in vitro* chromosome aberration in human lymphocytes and *in vivo* mouse micronucleus were all negative. Additional data from the literature investigating the mutagenic potential of melatonin and 6-hydroxymelatonin using a reduced Ames test (three strains of *Salmonella typhimurium*) concluded also that both molecules were not mutagenic (Neville et al, 1989, *Journal of Pineal Research, 6:73-76*). Further literature data report that melatonin and two related compounds, 6-hydroxymelatonin, the principal metabolite of melatonin, and 5-methoxyindoleacetric acid (5-MIAA) were screened for relevant information associating these chemicals with respect to mutagenic or carcinogenic effects (DEREK system). No structural alerts were identified. Overall, it is concluded that melatonin does not present any genotoxic potential.

Carcinogenicity

The dose levels of melatonin for the oncogenicity segment of the combined toxicity/oncogenicity study were 15, 75 and 150 mg/kg/day administered orally by gavage for 104 weeks. With regard to tumouri-genic potential, an increase in thyroid follicular cell neoplasia was observed in males at 150 mg/kg/ day, but was not statistically significant. Additional investigation of potential mechanism of action was conducted in a follow-up study using blood samples from this study (1829/007). An increase in the incidence of pituitary adenomas did reach statistical significance (p=0.036) in males at 150 mg/kg/ day. Thyroid follicular cell hypertrophy and a slight increase in thyroid follicular cell neoplasia were observed in males in the combined toxicity and oncogenicity study (1829/001). Although the increase in thyroid follicular cell neoplasia following exposure to high doses of melatonin (150 mg/kg/day) was not statistically significant, available blood samples from rats in that study were examined for plasma levels of TSH, T3 and T4, in order to try to clarify the mechanism for increased thyroid tumours. Comparison of mean TSH levels recorded on day 91 with mean TSH levels recorded on day 1 for the three male rats of the high dosage group (melatonin 150 mg/kg/day) for which blood samples were available indicated that there was an increase of +97% in the mean TSH levels of these animals at day 91, these males had also minimal hepatic centrilobular hypertrophy with minimal to slight inflammatory cell foci. The available TSH data, although limited in terms of animal numbers, supports the mechanism of action: liver enzyme induction leading to accelerated metabolic elimination of thyroxine and consequent TSH release. Plasma TSH levels at weeks 78 and 104 and the associated pathology from rats in the 104-week rat carcinogenicity study indicated no clear dose-related trends in plasma TSH levels in rats of either sex and there did not appear to be any positive correlation between plasma TSH and the associated thyroid or liver pathology in individual animals. The absence of dose related trend in plasma TSH levels supports the mechanism of action proposed that adaptive change in the liver following prolonged exposure to melatonin occurred, thus, it would be expected that the accelerated metabolism of thyroxine would have reduced or ceased by week 78 and the stimulus to potentiate TSH release would similarly have declined. The data from this study on TSH, T3 and T4 does not suggest any effect of melatonin on the levels of these hormones. Oral administration of melatonin up to 180 mg/kg/day for 26 weeks to hemizygous Tg rasH2 mice was found to be non-carcinogenic. Combined these data provide reassurance that melatonin does not show tumourigenic potential.

Reproductive and developmental toxicity

Fertility and early embryonic development

24 rats/sex/dose were treated orally by gavage with 0, 15, 55 or 200 mg/kg/day of melatonin.

There were no reports of effects on embryo-foetal development following the treatment of the premated rats at the doses used. The mean incidence of pre-implantation loss in the high dose group (15%) was greater than that of concurrent controls (7.5%) and outside the recent background control range (8.7% to 14.5%) but the values did not show statistical difference. Post-implantation loss was not affected by the treatment. The oestrous cycle, mating performance and fertility were not changed by treatment. Also the sperm number, motility and morphology were unaffected by the treatment.

It is known from the literature, that in many mammals, melatonin controls the reproductive cycle. Melatonin influences the levels of LH and FSH across many species. In women it can inhibit ovulation (Voordouw, 1992, *J.Clin Endocrinol and Metab; 74(1):108*).

Embryo-foetal development

Rat Developmental Toxicity

In a NTP rat study, melatonin was administered by gavage to 25 timed-mated CDR female rats on

gestation day 6 to 19, at doses of 50, 100 and 200 mg/kg/day. No maternal deaths were observed and the clinical signs reported were classified as minimal. Transient reduction of the body weight gain and relative decreased food intake were observed at the high dose group. Increased relative maternal liver weight was also observed in the animals from mid and high dose. Absolute liver and gravid uterine weights were not affected. The endpoints related to embryo/foetal growth, viability or morphological development were not modified by melatonin treatment. Based on the lack of embryo/foetal toxicity, the developmental toxicity NOAEL of melatonin was considered as 200 mg/kg/day. Based on the slight maternal toxicity reported at 200 mg/kg/day treated animals, the maternal toxicity NOAEL was considered as 100 mg/kg/day.

Rabbit Developmental Toxicity

A study of the embryo-foetal development in the NZW rabbit was performed by the applicant with oral administration of melatonin at 0 (control), 15, 50 and 150 mg/kg/day from days 7 to 19 of gestation. There were no dose-related maternal effects at any dose. No effects were observed on pre or post-implantation loss and mean number of foetuses/female. Foetal, litter and placental weighs were not affected by treatment. Visceral and skeletal malformations and/or variations were observed in all groups including controls. Some of such malformations/variations showed a trend or a significant increase in the treated groups, such as absence of lung or iliac alignment/caudal shift of vertebrae at high dose corresponding to an approximate AUC of 24000 to 45000 ng.h/ml. When compared to the AUC values to be achieved in man (<4 ng.h/ml), very high exposure ratios were reached in this study. An abundant literature can also be found, addressing the effects of melatonin in the reproductive function, using oral or subcutaneous route in several species, many of them in seasonal breeders or in cattle where melatonin is used to influence the reproductive process through a control of the oestrus cycle.

Prenatal and postnatal development, including maternal function

24 pre-mated rats were treated with 0, 15, 55 and 200 mg/kg/day of melatonin from Day 6 of gestation to Day 21 post-partum, inclusive. The treatment had no effect on parturition and outcome of pregnancy but the subsequent growth and viability of the high dose offspring was slightly reduced during lactation. At weaning, a slight reduction of offspring maturity was observed in all dose groups, but the subsequent F1 development was not modified. Therefore, melatonin intake during lactation is to be avoided. This is reflected in the SPC (section 4.6).

Juvenile toxicity

A GLP-compliant 14 day juvenile toxicity study was conducted to determine MTD of melatonin to define dose levels for a subsequent definitive juvenile toxicity study. No mortality was observed during the treatment and no animal was sacrificed moribund. No melatonin-related effects were observed for any of the in-life parameters, organ weight or macroscopic findings. Doses used in the juvenile toxicity study were close to those used in the chronic toxicity study in adult rats (study 1829/001). Based on the microscopic finding of non-reversible minimal increase in extramedullary hematopoiesis in the spleen at 160 mg/kg/day the NOAEL was determined to 80 mg/kg/day. A GLP-compliant 70 day repeat-dose toxicity study was conducted to determine the systemic toxicological and toxicokinetic profile of melatonin following daily oral administration to juvenile male and female rats and to evaluate the reversibility of any effects observed following a 14 day recovery period. No mortality was observed during the treatment and no animal was sacrificed moribund. No melatonin-related effects on clinical signs, body weight, food consumption, ophtamology, estrous cyclicity, sexual maturity, sperm parameters or macroscopic changes were observed. Significantly higher percentage of abnormal sperms at all doses and up to 5% at low and mid dose and up to 9% at high dose was observed. However, this raises no cause of concern as historical percentages up to 21.5% has been reported by the contract laboratory in control animals of the same strain. Melatonin-related reversible increases in reticulocyte count and total bilirubin were observed in females dosed with 160 mg/kg/day. Reversible increases in liver weight were observed in males and females dosed with 160 mg/kg/day. At 160 mg/kg/day a reversible increased splenic weight was observed in females. Non-reversible extramedullary hematopoiesis in spleen was observed in females given 160 mg/kg/day. Under the conditions of the study the NOAEL of melatonin in juvenile male and female rats was considered to be 80 mg/kg/day, which is accepted. TK data from the 70 day juvenile toxicity study showed that AUC_{last} increased with dose in a greater than dose proportional manner between 20 and 80 mg/kg, but in a dose-proportional manner between 80 and 160 mg/kg. Upon repeated dosing a 50% drop in exposure (day 70) compared to the exposure after single administration (day 1) was observed in both males and females as determined by the decreased AUC_{last} values. No notable gender differences were observed. Compared to the exposure of melatonin in adult rats melatonin exposure in juvenile rats was higher at similar dose levels, but the NOAEL in both age groups was observed at similar exposures. As physiological melatonin levels in mouse plasma ranges between 0.026-10 ng/ml and 0.070-20 ng/ml in rats, it is concluded that exposures to melatonin were significantly increased in the juvenile toxicity studies with rats in comparison to endogenous levels of these animals. The Applicant has provided supporting bibliographic data on saliva:plasma or serum concentration ratios showing a reliable and consistent range of about 1:3, regardless of whether the source of the melatonin was from endogenous production or exogenous intake. In addition, the saliva:plasma concentration ratio is also currently being assessed as part of an on-going clinical trial [CHDR1742]. The measured saliva:plasma geo-mean ratios of melatonin between C_{max}, AUC_{last} and AUC_{inf} were 0.35, 0.30 and 0.36 respectively, which is similar to what is reported in the provided bibliographic data. Consequently, the calculated safety exposure margin provided by the Applicant is both considered appropriate and sufficient.

2.7.4. Ecotoxicity/environmental risk assessment

Table 1 Summary of main study results

Substance (INN/Invented Name): melatonin			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.18 ± 0.12	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.18 ± 0.12	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0033	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.7.5. Discussion on non-clinical aspects

The results of primary pharmacology studies are difficult to interpret and extrapolation to humans cannot explain the clinical efficacy of the proposed dose in children of 1-5mg/day. In a literature study performed in diurnal macaque monkeys 5 µg/kg of melatonin administered 2 hours before the onset of darkness was the minimum effective dose to promote sleep onset. The plasma levels obtained were similar to the physiological ones in that species (54 pg/ml). Therefore, the efficacy of melatonin is based mainly on clinical information.

2.7.6. Conclusion on the non-clinical aspects

There are no objections to an approval of Slenyto from a non-clinical perspective.

2.8. Clinical aspects

2.8.1. Introduction

GCP

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

2.8.2. Pharmacokinetics

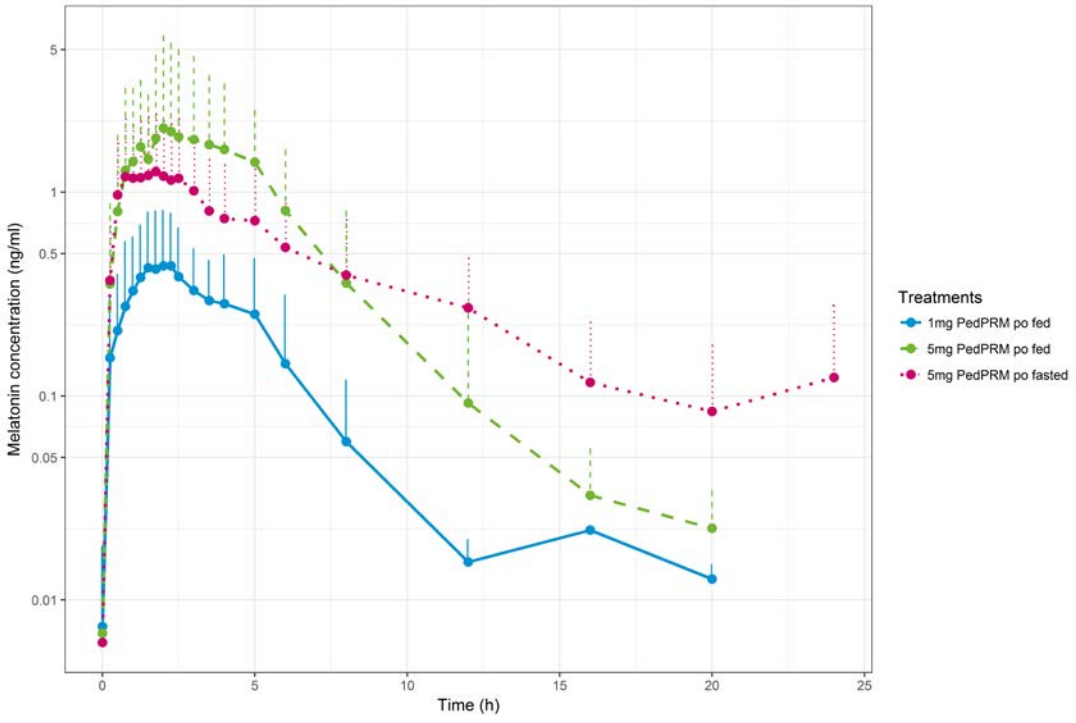
The submitted dossier includes one PK study (CHDR1219) with the applied Slenyto prolonged release tablet in children using saliva concentrations and one single dose, randomized, four-way cross-over, bioavailability and food interaction study of applied Slenyto prolonged release tablets (Slenyto) and Circadin tablets in healthy volunteers (NEU_CH_BE_27/ CHDR1742). In addition, four PK studies and two PK drug interaction studies with Circadin 2 mg tablet in healthy volunteers was submitted. Two *in vitro* studies have also been submitted, one protein binding study and one CYP inhibition and induction study. All studies except study CHDR1742 (NEU_CH_BE_27) have been assessed previously, the studies with Circadin in the approval of Circadin 2 mg tablet and the study with Slenyto tablet in children (CHDR1219) was submitted in 2014 according to Article 46.

Absorption

Melatonin has a low oral bioavailability, in the range 10-20%, and is associated with high inter-individual variability due to extensive first-pass metabolism. The Circadin prolonged release 2 mg tablet had a slower rate of absorption and a lower peak plasma concentration, but a greater overall extent of absorption than the melatonin solution. Following administration of Slenyto 5mg prolonged-release tablet in fed conditions the tmax was delayed, the data showed a significant food effect on the Cmax (51% reduction) but only minor on AUC (14% reduction) compared to fasted conditions.

As mean AUC(0-τ) after a single dose covers more than 90% of mean AUC(0-∞) for both Slenyto 1 mg and 5 mg and Circadin 2 mg, a low extent of accumulation is expected.

Figure 3: Mean with standard deviation concentration-time profiles of melatonin in plasma per treatment on a semi-log scale



Saliva measurements

Correlation analysis between saliva and plasma concentrations:

The uncorrected PK melatonin values were used for the correlation between saliva and plasma melatonin PK levels, since no baseline data was available for the saliva. The Spearman correlation coefficient was calculated. The Cmax, AUC0-last and AUC0-∞ measured in saliva and plasma samples following a single dose of 1 mg Slentyo showed a positive correlation, with correlation coefficients of 0.660 (Cmax), 0.825 (AUC0-last) and 0.929 (AUC0-∞).

Distribution

The serum protein binding of melatonin is 61.6% and independent of the concentration tested.

A correlation between plasma and saliva was established in study CHDR1742 (NEU_CH_BE_27) and the relationship was in similar range as observed in the literature (approximately 1:3 (36% for AUCinf and 30% for AUCt))

Elimination

A half-life of 40-50 min following immediate release formulations of melatonin is reported in the literature. The terminal saliva half-life following administration of Slenyto prolonged release tablets in study CHDR1219 was 4.4-4.9 hours. The plasma half-life following Circadin tablet (3.1-3.7 hours) was longer compared to melatonin solution (1.6-1.9 hours) in study 625/22940. The longer half-life following administration of prolonged release formulations compared to immediate release would indicate some absorption rate limitation or “flip-flop” pharmacokinetics.

Melatonin is metabolised by the hepatic cytochrome P450 system mainly to 6-hydroxymelatonin, followed by conjugation with sulphate (70%) or glucuronic acid (30%). Two % is excreted unchanged in the urine as melatonin.

The in vitro data suggest that 6-hydroxylation, the main metabolic pathway of melatonin, is mediated mainly, but not exclusively, by CYP1A2, the high-affinity enzyme involved in melatonin metabolism. This has also been confirmed in vivo with CYP1A2 inhibitors. Further, the involvement of CYP2C19 and CYP2C9 cannot be excluded.

Dose linearity

The applied product 1 and 5 mg was tested for dose proportionality in the new submitted study NEU_CH_BE_27 / CHDR1742. The point estimate of the slopes for C_{max}, AUC0-∞ and $AUC_{0\text{-last}}$ were 0.98 (90% CI 0.85, 1.11), 0.91(90% CI 0.82, 1.01) and 0.91 (90% CI 0.84, 0.98), respectively.

Pharmacokinetics in target population

Study CHDR1219: A single ascending dose crossover study has been conducted using the Slenyto prolonged-release tablets to assess the PK in 16 children with neurodevelopmental disorders and sleep disturbances. Baseline saliva melatonin concentrations were characteristic of daytime sampling, being low in the morning and increased over 12 hours towards the evening yet showing overall low endogenous levels. Saliva was sampled pre-dose and 1, 2, 3, 6, 10, 14 and 24 hours after administration.

Results:

Table 2: Summary of Melatonin PK Parameters (saliva concentrations) in PK Population

Treatment	N	C_{max} (pg/mL)	T_{max} (h)	AUC_{0-last} (pg.h/mL)[a]	$AUC_{0-\infty}$ (pg.h/mL)[a]	$t_{1/2}$ (h)[a]
2 mg	14	965 (1,170)	1.57 (0.762)	2,370 (1,240)	2,420 (1,100)	5.74 (3.31)
10 mg	14	3,970 (2,830)	1.37 (0.640)	12,400 (7,790)	13,300 (7,680)	4.44 (1.69)

Data are arithmetic means (and SD).

a Some subjects were excluded from the summary as the lambda z could not be accurately estimated for these individuals.

In the sub-analysis population that excluded the 3 subjects who were thought to have held the tablets in their mouths, the saliva concentration-time profile of melatonin was also characterised by rapid absorption and disposition.

Table 3: Summary of Melatonin PK Parameters (saliva concentrations) in the Sub-Analysis Population

Treatment	N	C_{max} (pg/mL)	t_{max} (h)	AUC_{0-last} (pg.h/mL)[a]	$AUC_{0-\infty}$ (pg.h/mL)[a]	$t_{1/2}$ (h)[a]
2 mg	11	410 (210)	1.73 (0.792)	1,960 (1,030)	2,150 (960)	4.87 (1.87)

Data are arithmetic means (and SD).

a Some subjects excluded from the summary as the lambda z could not be accurately estimated for these individuals.

Special populations

Melatonin is mainly cleared by metabolism. Melatonin concentrations were significantly higher in subjects with liver cirrhosis compared to healthy subjects. A study on patients with end stage renal disease under chronic haemodialysis showed that melatonin plasma concentrations were comparable to the ones from healthy subjects. However, other stages of renal insufficiency not compensated with haemodialysis have not been studied. Therefore there is no evidence that renal insufficiency does not affect melatonin elimination. Melatonin exposure seems to be higher in females than in males. There is no submitted data regarding weight and age (2-18 years).

2.8.3. Pharmacodynamics

The Applicant has not conducted any new PD studies for the current application. The summary on pharmacodynamics is based on a review of the literature.

Primary pharmacology

Mechanism of action

Melatonin (N-acetyl-5-methoxytryptamine) is the major hormone produced by the pineal gland. It is a lipid soluble substance with low molecular weight and is structurally related to serotonin and its precursor, the amino acid tryptophan. Melatonin plays a major role in the entrainment of the biological clock and in mediating the sleep wake cycle (Kveder and McIsacc, 1961; Dawson and Encel, 1993).The concentration of the hormone in blood is increased during the hours of darkness, while a low concentration occurs during the day (Wurtman, 1986). The function of melatonin has been extensively investigated in animals and humans. Because of its possible role in influencing the circadian rhythm of sleep, melatonin has been used for treating sleep disorders including, jet-lag, shift work, delayed sleep phase syndrome, periodic sleep disorder in blindness and sleep and behavioural disorders in children with multiple brain damage (Deacon and Arendt, 1995; Brzezinski, 1997).

Effect on body temperature

A significant dose-response relationship between the dose of oral melatonin, the magnitude of temperature suppression and the degree of advance in phase shift in melatonin rhythm has been observed (Deacon and Arendt, 1995). Dose-response data indicate that the melatonin dose needed to elicit maximal temperature lowering, sleep induction and circadian phase-shifting effects is in the range of 0.5-5 mg. Higher doses (10 mg and 40 mg) also suppressed the normal diurnal rise of core body temperature (Hughes and Badia, 1997).

No adverse events specifically relating to temperature effects have been reported following prolonged use of 5 mg melatonin for 6 months (Arendt and Deacon, 1997). This may be due to normal body temperature being lower at night as part of the circadian rhythm of body temperature, which is regulated by the endogenous biological clock.

Effects on endogenous melatonin secretion

Several studies in human volunteers have demonstrated that administration of exogenous melatonin does not affect the peak and total amount of the endogenous melatonin secretion profile (Wright et al, 1986; Mallo et al, 1990; Matsumoto et al, 1997; Lissoni et al, 1999). If the timing of melatonin administration is optimised according to the melatonin phase response curve, it is possible that consistent phase advances and delay can be achieved (Lewy and Sack, 1997).

Effect on circadian rhythm

Melatonin administration at doses of 5 mg can reduce the effects of jet lag and advance sleep phase in delayed sleep phase syndrome and synchronise the sleep wake cycle in blind and brain damaged children (Dahlitz et al, 1991; Dawson and Armstrong, 1996; Skene et al, 1996; Palm et al, 1997; Skene et al, 1999; Jan et al, 1999). Jet lag symptoms were significantly reduced after an eastbound flight across eight time zones in a placebo-controlled study. Melatonin produced shorter sleep latency, improved sleep quality and more rapid synchronisation of melatonin and cortisol secretion to the new time zone (Cagnacci et al, 1997; Palm et al, 1997). Other data support these findings (Samel et al, 1991; Suhner et al, 1998). In a recent study, short-term administration of suitably timed sustained-release melatonin (1.5 mg) phase-shifted circadian rhythms and redistributed activity during a 16-hour sleep opportunity, with no evidence of effects on endogenous melatonin secretion or pituitary/gonadal hormones (Rajaratnam et al, 2003).

Secondary pharmacology

Effects on reproductive and other hormones

Melatonin levels are normal in the menstrual cycles of healthy women (Brzezinski et al, 1988) but elevated in those with amenorrhea (Berga et al, 1988; Laughlin et al, 1991; Kadva et al, 1998). High doses can suppress the luteinising hormone (LH) surge in young women and partially inhibit ovulation (Voordouw et al, 1992).

Increased levels are found in men with hypogonadotrophic hypogonadism suggesting that increased androgen secretion may affect melatonin metabolism (Luboshitzky et al, 1996a; Luboshitzky et al, 1996b).

A company sponsored double-blind placebo controlled study (Study 951003) investigated the effect of melatonin (5 mg, in a prolonged release formulation), given double-blind for 6 months and then single-blind for additional 12 months to 57 men with benign prostatic hyperplasia (BPH). The results indicated the melatonin has no significant effect on prostate size, nor was there an effect on LH, testosterone, dihydrotestosterone (DHT), prolactin or oestradiol levels (Luboshitzky et al, 1996b).

The company has sponsored a meta-analysis in an effort to reveal trends, if any, of the effects of melatonin on the hypothalamic-pituitary-adrenal (HPA)/ hypothalamic-pituitary-gonadal (HPG) hormones (Schmidhauser, 2004). Results were analysed by subgroups for subjects and adjusted for different dose levels. In order to provide meaning to this analysis, it was first necessary to define the accepted normal ranges for the hormones of the HPA/HPG axes and then compare those with the ranges observed. Table 1 presents the normal adult ranges for the major hormones of the HPA/HPG axes, as well as the ranges found in control and melatonin-treated subjects. The accepted ranges have been reproduced from the Medical Testing Protocols as published by Labcorp, Laboratory Corporation of America (http://www.labcorp.com/datasets/labcorp/html/chapter/).

As can be seen in Table 1, the administration of melatonin in various doses did not significantly influence the levels of these hormones. All remained well within their respective normal ranges. Taken together, there is no evidence in the literature suggesting that exogenous melatonin, at doses similar to those of Neurim's prolonged-release formulation and even at five-fold higher, affects the HPA and HPG pathways in ways other than mimicking those seen normally at night when melatonin is produced endogenously. Moreover, to show any effects of melatonin on HPA and HPG pathways, melatonin has to be given at daytime, namely when it is not present endogenously, and even under these conditions it only demonstrates effects resembling the physiological changes that occur at night in nature and magnitude.

Table 4 Normal and Observed Ranges of Hormone Levels of the HPA/HPG Axes

Measured Hormone	Normal Range For Adult Females	Normal Range For Adult Males	Ranges Found: Melatonin-treated subjects	Ranges Found: Placebo treated subjects
Prolactin (ng/ mL)	1.8 – 29.2		10.26 – 26.9	8.0 – 12.5
		2.17 – 17.7	5.20 - 10.2	3.98 – 8.1
LH (U/L)	0.5 – 16.9		3.9 – 6.6	4.5 – 6.9
		1.5 – 34.6	2.6 - 12.9	2.4 – 10.8
FSH (U/L)	1.5 – 33.4		5.2 – 6.1	4.5 – 6.6
		1.4 – 18.1	2.0 – 4.1	2.0 – 4.5
GH (mU/L)	0 – 20	0 - 20	2.0– 14	0.8 – 10.6
Cortisol(ug/mL)	4.3 – 22.4	4.3 – 22.4	4.5 – 20	5 – 19.3

Pharmacodynamic interactions with other medicinal products or substances

Benzodiazepine and Non-benzodiazepine hypnotics

Melatonin could potentially augment benzodiazepine and also non-benzodiazepine hypnotics that exert their effects via the GABA-A receptor (Ferini-Strambi et al, 1993; Garfinkel et al, 1999) though not via the benzodiazepine binding sites since melatonin's hypnotic action is not mediated via these receptors (Nave et al, 1996). It can potentiate the GABA-A receptor in the SCN via the MT1 receptors, while inhibiting it in the hypocampus via the MT2 receptor (Wan et al, 1999). In healthy male subjects, a single dose of diazepam (10 mg) or alprazolam (2 mg) suppressed the nocturnal rise in plasma melatonin (McIntyre et al, 1993). Similarly, repeated administrations of flunitrazepam resulted in nocturnal suppression of melatonin, and sometimes resulted in a rebound of daytime melatonin output (Kabuto et al, 1986). However, chronic antidepressant treatment with adinazolam did not alter 6-sulphatoxy melatonin (6-SMT) output in female depressed patients (Kennedy and Brown, 1992). Similarly, bedtime administration of triazolam in humans has no major effects on melatonin (L'Hermite-Baleriaux, 1987). A pharmacodynamic (PD) interaction between Circadin and zolpidem was found in a Neurim sponsored study (NEU 112001). This PD interaction was associated with an impairment of reaction time (mainly 1 hour post-dosing) and driving abilities (2 hours post-dosing) and memory (emphasised particularly at 1 hour post-dosing). Thus caution should be exercised if co-prescription is necessary. The co-administration of Circadin 2 mg and zolpidem (a non-benzodiazepine hypnotic drug) provided clear evidence for a marked transitory PD interaction between Circadin 2 mg and zolpidem 1 hour following co-dosing (Study NEU 112001). Zolpidem caused significant impairment of vigilance memory and driving skills in subjects 55 years old and older compared to placebo. Circadin 2 mg had no such effect, but concomitant administration greatly potentiated the zolpidem-induced impairment of attention, memory and coordination compared to zolpidem alone. The co-administration of 10 mg zolpidem with Circadin 2 mg did not alter either the plasma melatonin or zolpidem concentrations. In an exploratory study, 34 volunteers with insomnia who had been long-term benzodiazepine users were enrolled in a placebo controlled benzodiazepine discontinuation trial that assessed the effects of concomitant Circadin (2 mg/day) compared to placebo in facilitating benzodiazepine discontinuation. Over a 6-week period, patients were to firstly reduce and then discontinue their habitual dose of hypnotic, while receiving either Circadin 2 mg or placebo, as allocated. The results indicated that Circadin 2 mg effectively facilitated discontinuation of benzodiazepine while maintaining good sleep quality during the taper period compared to placebo. By the end of the tapering period, sleep quality scores were significantly higher in the Circadin 2 mg group than for the placebo group. This effect is most likely due to the potentiation by melatonin of the hypnotic effects of benzodiazepine and provides further evidence for the efficacy of Circadin 2 mg in chronic insomnia patients.

Adrenergic Agonists and Antagonists

The administration of clonidine, a central α2-agonist, decreases nocturnal plasma melatonin, while administration of the selective α2-antagonist, idozoxan, increases it (Grasby et al, 1988). This is presumably mediated by effects on the presynaptic inhibitory α-2-receptors of the superior cervical ganglion terminals in the pineal gland. Clonidine has been reported to occasionally cause insomnia, consistent with its effect on melatonin.

Administration of the ß-1 adrenergic antagonist atenolol (100 mg) to healthy subjects at 18:00 hours resulted in the abolition of the nocturnal excretion of 6-SMT in the urine. The administration of either propranolol (60 mg at 18:00 hours followed by 40 mg at 22:30 hours) or atenolol (50 mg at 18:00 hours followed by 25 mg at 22:30 hours) abolished the nocturnal melatonin excretion in healthy males (Demitrack et al, 1990). In hypertensive patients, chronic treatment with atenolol (mean dose 86 mg/day), propranolol (mean dose 305 mg/day) or metoprolol (mean dose 197 mg/day) for four weeks reduced melatonin excretion, but the effect was significant only for the metoprolol group (Brismar et al, 1988). In the metoprolol group, a significant relationship ($p<0.05$) was found between the decline in melatonin and the increase in sleep disturbance, suggesting the CNS side-effects during beta-blockade are related to a reduction of melatonin levels.

Alcohol

Alcohol directly inhibits pineal gland function (Rojdmark et al, 1993; Schmitz et al, 1996). Circadin 2 mg affects sleep significantly more in regular compared to occasional alcohol drinkers (Study 30424). Co-administration with antidepressants did not affect depression scores (Rosenthal et al, 1986) but melatonin did improve the sleep pattern without affecting depressive symptomatology when co-prescribed with fluoxetine (Dolberg et al, 1998). Melatonin reversed alcohol-induced increased core temperature and sleep onset latency.

Doses of 0.52 g/kg ethanol given in the evening inhibited nocturnal melatonin secretion by approximately 20%. Lower doses (0.34 g/kg) of ethanol lacked any such effect. Urinary excretion of melatonin was unaffected by either dose level of ethanol (Rojdmark et al, 1993).

Antidepressant Drugs

Tricyclic antidepressants which inhibit norepinephrine uptake (e.g. desmethylimipramine, desipramine, imipramine) acutely exaggerate the increased pineal cyclic adenosine monophosphate (cAMP) synthesis produced by catecholamines and thereby increase melatonin. Chronic use of such drugs may alter both the number and sensitivity of adrenergic receptors. Some human studies have shown persistent elevation of plasma melatonin during treatment with tricyclic antidepressants, others have not (Checkley and Palazidou, 1988). Blockade of monoamine oxidase (MAO) increases the amount of available norepinephrine by reducing its catabolic degradation. The antidepressant, tranycyromine (non-selective MAO inhibitor), and clorgyline (MAO-A selective inhibitor) elevate melatonin both acutely and chronically in humans, while the selective MAO-B inhibitor deprenyl does not (Murphy et al, 1986). This is most likely due to the fact that the noradrenergic fibres in the pineal gland apparently contain mostly MAO-A (Checkley and Palazidou, 1988).

The co-administration of 75 mg imipramine (tricyclic antidepressant) with Circadin 2 mg did not change the PK of melatonin (Report RD 625/22964). Furthermore, the co-administration did not change the PK of either imipramine or desipramine. However, co-administration induced a stronger feeling of incompetence as measured by the Lader-Bond questionnaire compared to the administration of either Circadin 2 mg or imipramine alone. Imipramine led to a greater feeling of troublesomeness compared to either Circadin 2 mg or the combined drug administration, suggesting a possible PD interaction between Circadin 2 mg and imipramine.

A recent report has shown that melatonin improved sleep of patients with major depressive disorder treated with fluoxetine, without affecting the rate of improvement of their depressive symptoms (Dolberg et al, 1998). Fluvoxamine, a selective serotonin reuptake inhibitor, has repeatedly been shown to elevate melatonin serum concentrations (Hartter et al, 2000). As fluvoxamine is known to inhibit several hepatic CYP P450 isozymes e.g, CYP1A2 (Anton-Tay et al, 1998) and CYP2C19 (Mailliet et al, 2004), the elevation effect of fluvoxamine on melatonin serum concentrations has been attributed to the inhibition of CYPs involved in the metabolism of melatonin (Hartter et al, 2000). In another study, fluvoxamine, but not citalopram, was shown to increase serum melatonin in healthy subjects. Unlike fluvoxamine, citalopram does not exhibit CYP inhibition and so these results support the role of CYP1A2 and CYP2C19 in the metabolism of melatonin (Von Bahr et al, 2000).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit prostaglandin synthesis in humans. Prostaglandins are involved in thermoregulation, melatonin synthesis and sleep. Administration of the NSAIDs, aspirin and ibuprofen, suppressed the normal nocturnal increase in melatonin and also attenuated the normal nocturnal decrease in body temperature (Murphy et al, 1996). The authors suggested that the NSAIDs effects on sleep and body temperature are related to prostaglandin synthesis inhibition and/or suppression of melatonin.

In humans, administration of ibuprofen, a blocker of prostaglandin synthesis, reduces melatonin levels in a dose-dependent manner. Early evening administration of 400 mg ibuprofen delayed the nocturnal surge in plasma melatonin (Surrall et al, 1987). In the same study, evening administration of a slow releasing preparation of indomethacin (75 mg) completely prevented the nocturnal rise in plasma melatonin. The effect appears to operate at the level of the pineal gland rather than at the oscillator.

2.8.4. Discussion on clinical pharmacology

Pharmacokinetics

One PK study was performed with the applied Slenyto 1 mg prolonged release formulation and was performed in children aged 7-18 years. Further, a single dose, randomized, four-way cross-over, bioavailability and food interaction study of Slenyto and Circadin in healthy male and female volunteers was submitted as response. The other submitted PK studies were performed with the Circadin 2 mg prolonged release formulation.

According to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) the pharmacokinetics should be characterised for a new modified release formulation in appropriate single dose and multiple dose pharmacokinetic studies. A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected. The Applicant has not performed any multiple dose study however justified the absence. Therefore waiver for multiple dose study is considered acceptable. Slenyto prolonged release formulation is considered dose-proportional between 1 and 5 mg since the results of the pre-defined calculations of dose-proportionality is nearly covered by the confidence limits and when comparing dose-adjusted mean AUC, the difference between 1 and 5 mg is no more than 25%. Therefore based on study results linearity between 1 mg and 5 mg dose can be concluded. Food effect was also evaluated for the highest applied strength 5 mg. The data showed a significant food effect on the Cmax (51% reduction) but only minor on AUC0-∞ (14% reduction) under fasted conditions. The Tmax was attained faster in fasted state (2.06 vs. 3.11 h).

The results of the PK study CHDR1219 in children was based on saliva sampling and no plasma concentration profiles were determined. The number of children was small, only 14 children in variable ages of 7-15 years were included and no PK data has been submitted for the younger children, 2-7 years. The results indicate a similar shape of the saliva concentration curve in this study compared to plasma concentration curves following administration of Circadin 2 mg depot tablet.

The correlation between saliva and plasma concentration was investigated for Slenyto. The literature was reviewed and showed that there is a relationship between plasma and saliva. In the submitted study CHDR1742 (NEU_CH_BE_27) a simultaneous measurements of plasma and saliva melatonin levels were included. A correlation between plasma and saliva was established and the relationship was in similar range as observed in the literature (approximately 1:3 (36% for AUCinf and 30% for AUCt))

The question is if “the simple way” of calculating plasma exposure from saliva data in children is valid (see Nonclinical) ie by just using the established relationship to calculate the saliva PK parameter from plasma.

It is concluded that saliva concentrations may be used as a substitute for plasma in children and the data using saliva could be recalculated in order to be able to use the obtained PK data for exposure margins comparison to the nonclinical program and further for the extrapolation from adult data.

The applicant discussed the elimination of melatonin and other compounds eliminated via CYP1A2 in children between 2-7 years of age as this age is not included in the PK study. Based on the literature it seem that the ontogeny of CYP1A2 is mature around 2-3 years of age where from the age of 2-3 years old, the rate of metabolism exceeds the adult rate and then it declines to adult rates at maturation.

Melatonin exposure seems to be higher in females than in males. However, no dose adjustment is needed since no pharmacodynamic differences were found. There is no submitted data regarding weight.

Pharmacodynamics

The mechanism of action of melatonin and its primary pharmacology are well-known, including its ability to dose-dependently reduce the body temperature, sleep induction and circadian phase-shifting effects is in the range of 0.5-5 mg.

The applicant has presented data from studies on adult females and males, showing no significant effects of administration of exogenous melatonin on the hypothalamic-pituitary-adrenal (HPA)/ hypothalamic-pituitary-gonadal (HPG) hormones.

However, the fact that melatonin plasma levels are high in prepubertal children and is dramatically reduced during puberty, has led to the suggestion that administration of exogenous melatonin leading to supraphysiological levels in pre-pubertal and pubertal children may lead to pubertal abnormalities. There is a lack of long-term safety studies in children investigating this issue.

The best study, with regards to pubertal development, was conducted by Geijlswijk et al. in 2011. They studied 51 children (mean age 12.0 years, 8.6-15.7 years) who took melatonin during a mean time of 3.1 years (min 1.0-max 4.6) at a mean dose of 2.69 mg (0.3-10 mg). The parents reported Tanner stages of their children (N=46) using a questionnaire and there was no substantial deviation of the development of the children with respect to puberty. A drawback of this study was the low number of subjects and that Tanner staging was reported through questionnaires from the parents and not directly investigated by the physicians. Nevertheless, it is reassuring that there is no data so far supporting the theoretical risk of hormonal disturbances or effects on the pubertal development from melatonin treatment. However, more long-term data is warranted.

The PD interactions section of the proposed SmPC is identical to the corresponding section of the Circadin SmPC. For melatonin, due to the lack of well-controlled interaction studies, it appears hard to distinguish which interactions are pharmacokinetic and which are pharmacodynamics. Not all interactions are relevant for children, but may be relevant for adolescents (e.g. alcohol, cigarette smoking). Thioridazine and imipramine were both withdrawn from the Swedish market in 2005. About 70% of the children in the child study used concomitant medication during the study, of which stimulants and/or antidepressants were used by around 30%, antipsychotics by around 10% (both classical and atypical neuroleptics), analgesics around 17% (mainly paracetamol and ibuprofen), systemic antibiotics (15%), asthma drugs (15%), antihistamines (14%), constipation drugs (13%), drugs for acid related disorders (7%), antiepileptics (6%). From the child study, it appears that tricyclic antidepressants are not commonly used in these children. If on antidepressant therapy, the child is taking an SSRI medication.

Beta blockers can reduce the levels of melatonin and should not be taken in the evening in order not to aggravate a sleep disturbance. If needed, these should be taken in the morning. The reports by Murphy et al. (1996) and Surrall et al. (1987) that prostaglandin synthesis inhibitors (NSAIDs) such as aspirin and ibuprofen, given in the evening may suppress the melatonin levels in the night by up to 75% may be of some concern, since anti-inflammatory analgesics are commonly used in these children (12% of the children in the study took ibuprofen). However, Surrall et al. was a small study with only 4 subjects, whereas Murphy et al. tested 54

subjects (13 aspirin, 20 ibuprofen, 21 placebo). These data appear not to have been confirmed in larger trials. The sleep hygiene measures before starting melatonin treatment may include avoidance of administration of NSAIDs and/or beta blockers in the evening, since these may blunt the night-time release of endogenous melatonin. The SmPC section 4.5 on Interactions has now been updated to include information on beta-blockers and NSAIDs to be avoided in the evening.

As pointed out by the applicant, the important relation between exposure and effect does not appear to be between plasma levels and sleep inducing effects but rather between CSF levels and effect. Thus, the applicant argues that a melatonin dose that generates 5-10 times the physiological plasma levels is needed to produce normal CSF levels and a clinically relevant effect on sleep.

2.8.5. **Conclusions on clinical pharmacology**

From a clinical pharmacology point of view other concerns have been formulated as outlined in the list of questions.

2.9. Clinical efficacy

Dose-response studies and main clinical studies

A randomized, placebo-controlled study to investigate the efficacy and safety of Slenyto to alleviate sleep disturbances in children with neurodevelopmental disabilities

Study design

Period	Wash-out Sleep Hygiene	Run-in, Single-blind		Double-blind				Open-Label								Run-out, Single-Blind	
Treat-ment	No drug inter-vention[1]	Placebo		Circadin® 2 mg or PBO		Circadin® 2 mg, 5 mg, or PBO		Circadin® 2 mg or 5 mg		Circadin® 2 mg, 5 mg, or 10 mg						Placebo	
Week	-4 to 0	1	2	3	5	6	15	16	28	29	41	42	54	55	106	107	108
Visit[3]	SCRN first day of Week -4, ±3 days	Visit 1 first day of Week 1, ±3 days	Visit 2 last day of Week 2, ±3 days random-ization/ baseline visit		Visit 3[2] last day of Week 5, ±3 days dose modi-fication		Visit 4 last day of Week 15, ±3 days		Visit 5[2] last day of Week 28, ±3 days dose modi-fication		Visit 6 last day of Week 41, ±7 days		Visit 7 last day of Week 54, ±7 days		Visit 8 last day of Week 106, ±7 days		End of Study last day of Week 108, ±3 days

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]). Sufficient patients were to be screened to allow 120 patients to be randomized in a 1:1 ratio to receive Slenyto or placebo.

Slenyto 1 mg tablets were used in this study. The tablets were 3 mm in diameter and allowed flexibility of dosing for the required dose titrations from 2 mg to 5 mg or 10 mg.

Dose escalation rules

At the end of the first 3 weeks of the double blind period, (Week 5, Visit 3) and 13 weeks of open-label treatment(Week 28, Visit 5), the investigator had to review the Sleep and Nap Diary (SND); if the patient had 6 hours or less of non-interrupted sleep (continuous sleep) and / or half an hour or more of sleep latency in 3 out of 5 nights in a week (as for diary compliance there had to be 5 nights out of 7 nights) for two weeks, then he would be eligible for dose escalation from 2 mg to 5 mg at visit 3, and/or 2 mg to 5 mg or 5 to 10 mg at visit 5.

As the mean of these variables had to be calculated for 14 nights before the visit, this was calculated by the electronic CRF that notified the investigator if the patient was eligible for dose escalation, or not.

In addition to this, a dose increase was allowed only if two safety conditions were met:

1. the patient had no SAEs related to study drug
2. the patient did not suffer from daytime fatigue related to study drug.

At any time, a patient's dose could be decreased to 2 mg or 5 mg for reasons such as AEs that were considered related to the study drug, and/or specifically for the following reasons:

• An unacceptable increase in daytime fatigue

• An unacceptable behavioral change

• If the patient stopped responding to study drug (sleep improved and then deteriorated on higher dose)

Primary efficacy measurement

The primary efficacy measurement was total sleep time, calculated from the Sleep and Nap Diary. The Sleep and Nap Diary was to be completed every morning by the parent/caregiver at home for 14 days prior to each visit during the first year of study treatment. Each diary entry was preferably to be made 2-3 hours after the child woke up each day.

Secondary efficacy measurements

Secondary efficacy measurements taken from the Sleep and Nap Diary were:

• 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.

• Number of dropouts during the 13-week (Week 15) double-blind treatment period.

• Assessment of sleep parameters by actigraphy:

Actiwatches were dispensed to patients at Visit 1 so that they could be worn for 14 days prior to Visit 2. The device was delivered to the patient's home no earlier than 3 weeks before Visit 4 to ensure that adequate battery strength was maintained. Actiwatches were to be worn for 14 nights before Visit 2 and Visit 4 and collected at Visit 2 and Visit 4. The Actiwatch was to be worn by the patient from drug-intake at night until lights on in the morning.

Exploratory efficacy measurements

Exploratory efficacy measurements included measurements recorded in the Sleep and Nap Diary

Other exploratory 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

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

• Caregiver's daytime sleepiness as assessed by the ESS

• Caregiver's well-being as assessed by the WHO-5 well-being questionnaire

• Caregiver's quality of sleep at night using the PSQI global score and components

The CSDI, CGAS, SDQ, ESS, WHO-5 and PSQI questionnaires were to be completed by the site coordinator/Investigator with the parent/caregiver's input.

Safety measurements

- Adverse events
- Physical examination and vital signs

The Tanner scale was used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference were used to stage children's development. Between the ages of 5 and 8 years, the children's physical development was determined using the BMI.

- Epilepsy assessment

In children diagnosed with epilepsy, the number and severity of epilepsy seizures during the study were recorded by the parents throughout the study in Epilepsy Seizures Diaries.

Demographic characteristics at screening (all randomized set)

	Circadin® (N=60)	Placebo (N=65)	Overall (N=125)
Age, years			
Mean ± SD	9.0 ± 4.08	8.4 ± 4.24	8.7 ± 4.15
Range	2, 17	2, 17	2, 17
Sex, n (%)			
Male	45 (75.0%)	47 (72.3%)	92 (73.6%)
Female	15 (25.0%)	18 (27.7%)	33 (26.4%)
Ethnicity, n (%)			
Not Hispanic or Latino	40 (66.7%)	49 (75.4%)	89 (71.2%)
Hispanic or Latino	12 (20.0%)	7 (10.8%)	19 (15.2%)
Other	8 (13.3%)	8 (12.3%)	16 (12.8%)
Unknown	0	1 (1.5%)	1 (0.8%)
Race, n (%)			
White	57 (95.0%)	55 (84.6%)	112 (89.6%)
Black or African American	1 (1.7%)	8 (12.3%)	9 (7.2%)
Other	3 (5.0%)	3 (4.6%)	6 (4.8%)
Asian	0	2 (3.1%)	2 (1.6%)
Height, cm			
Mean ± SD	133.4 ± 24.17	130.4 ± 27.20	131.8 ± 25.73
Range	89, 180	79, 197	79, 197
Weight, kg			
Mean ± SD	37.86 ± 21.495	35.22 ± 23.249	36.49 ± 22.374
Range	11.7, 90.1	9.8, 129.9	9.8, 129.9
BMI, kg/m^2			
Mean ± SD	19.50 ± 4.899	18.79 ± 4.901	19.13 ± 4.893
Range	12.7, 32.8	12.3, 35.3	12.3, 35.3

BMI = body mass index; SD = standard deviation
Data source: Table 14.1.2.2

Medical history and concurrent illnesses

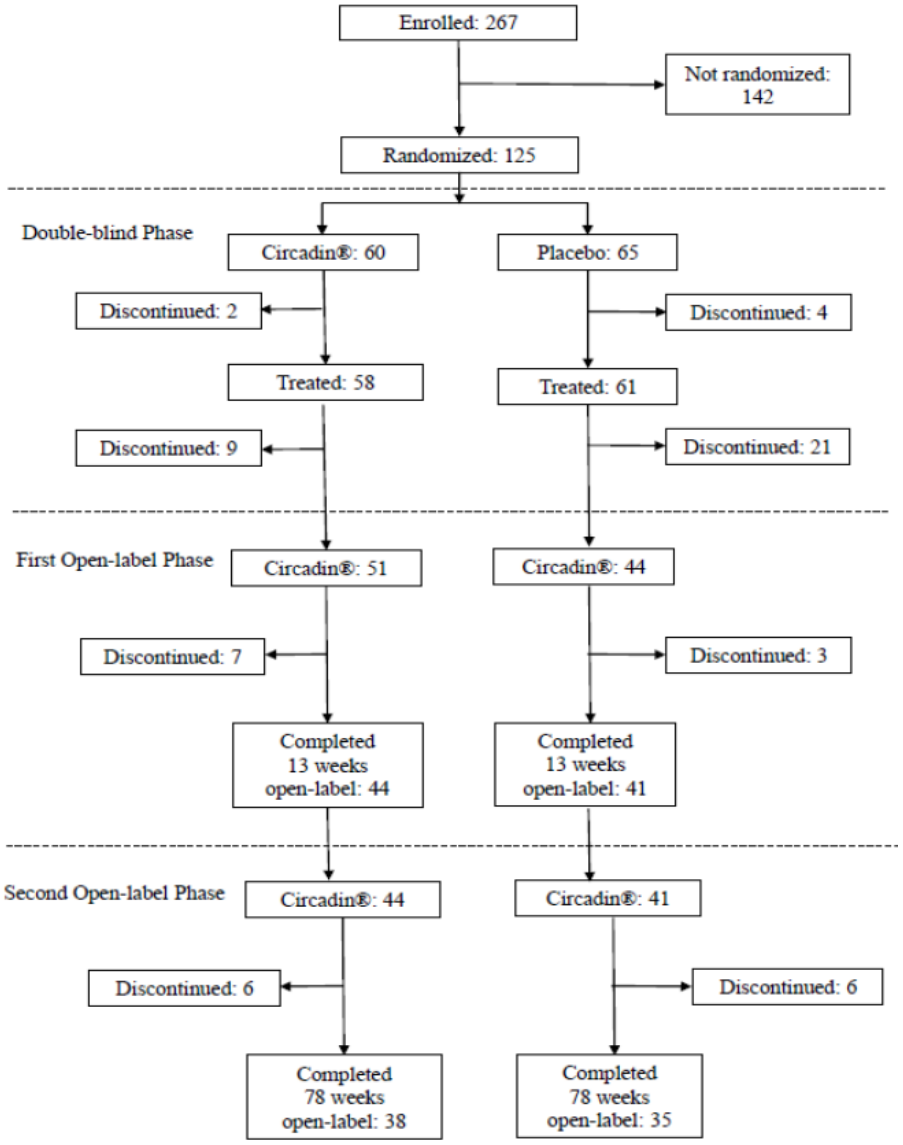
In total, 98.4% patients reported at least one medical history. There were no notable differences between the groups with regard to medical history. Most patients reported a history of psychiatric disorders (90.4%), with the most common preferred terms being agitation (70.4%) and mood swings (66.4%). 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%). Under the SOC 'General disorders and administration site conditions", 56.8% patients reported fatigue.

Prior and concomitant medications

Prior medications were reported for 46 (36.8%) patients. The most commonly reported prior medications were melatonin (15.2%) and paracetamol (9.6%). Although melatonin was reported on the prior medication eCRF for only 15.2% of patients, it is apparent from the melatonin use data that over half the patients (65.6%) had taken melatonin prior to study entry.

During each phase of the study, approximately 70% of patients took at least one concomitant medication. The most commonly reported medications were: psychoanaleptics (30.4% and 33.7%), analgesics (17.6% and 14.7%), antibacterials for systemic use (15.2% and 15.8%), drugs for obstructive airway diseases (15.2% and 18.9%), antihistamines for systemic use (13.6% and 18.9%), and drugs for constipation (12.8% and 17.9%) (% in brackets are for the double-blind and open-label phases, respectively). The overall profile of concomitant medications was similar between treatment groups within each phase.

Participant flow



Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial NEU_CH_7911

Title: A randomized, placebo-controlled study to investigate the efficacy and safety of Slenyto to alleviate sleep disturbances in children with neurodevelopmental disabilities			
Study identifier	**1.** NEU_CH_7911		
Design	Randomized, placebo-controlled		
	Duration of Run-in phase:		4-week, basic sleep hygiene and behavioral intervention period combined with wash-out period of previous sleep medication (if required), followed by a 2-week single-blind placebo run-in period (Weeks 1 to 2).
	Duration of main phase:		13 weeks, randomized, placebo-controlled
	Duration of Extension phase:		13-week open-label period (reported within this application) 78-week open-label follow-up period and 2-week placebo run-out period (still ongoing, no data reported yet)
Hypothesis	Superiority		
Treatments groups	Slenyto		Slenyto. Starting dose 2 mg, after 3 weeks optional dose increment to 5 mg, duration: 13 weeks. number randomized=60 subjects
	Placebo		Placebo, 13 weeks, number randomized=65 subjects
Endpoints and definitions	Primary endpoint	Total sleep time (TST)	assessed by the Sleep and Nap Diary after 13 weeks of treatment
	Secondary endpoint	Sleep latency	assessed by the Sleep and Nap Diary after 13 weeks of treatment
	Secondary endpoint	Duration of wake after sleep onset	assessed by the Sleep and Nap Diary after 13 weeks of treatment

	Secondary endpoint	Number of awakenings	assessed by the Sleep and Nap Diary after 13 weeks of treatment
	Secondary endpoint	Longest sleep period	assessed by the Sleep and Nap Diary after 13 weeks of treatment
	Secondary endpoint	Total time in bed per night	assessed by the Sleep and Nap Diary after 13 weeks of treatment
	Secondary endpoint	CSDI score	Sleep disturbance as assessed by the CSDI score
	Secondary endpoint	CGAS	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.
	Secondary endpoint	SDQ	Behaviour at home and in school as assessed by the SDQ. The SDQ was completed by the site coordinators/Investigators by interviewing the parents/caregivers
	Exploratory endpoint	ESS	Caregiver's daytime sleepiness as assessed by the ESS
	Exploratory endpoint	WHO-5	Caregiver's well-being as assessed by the WHO-5 well-being questionnaire
	Exploratory endpoint	PSQI	Caregivers' quality of sleep at night as assessed by the Pittsburgh Sleep Quality Index (PSQI)
Database lock	(study ongoing)		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Full analysis set Change from baseline to week 15

Descriptive statistics and estimate variability	Treatment group	Slenyto	Placebo
	Number of subject	52	48
	Total sleep time (min) *(adjusted treatment mean)*	+51.16	+18.73
	95% CI	[+30.42, +71.90]	[-2.72, +40.19]
	Sleep latency (min) *(adjusted treatment mean)*	-37.88	-12.58
	95% CI	[-51.40, -24.36]	[-26.47, +1.31]
	Wake time after sleep onset (min) (change from BL)	-13.70	-7.77
	SD	± 29.945	± 15.399
	Number of awakenings per night (change from BL)	-0.30	-0.23
	SD	± 0.696	± 0.757
	Longest sleep period (min) (change from BL)	+77.93	+25.45
	SD	± 127.322	± 95.600
	Total time in bed per night (min) (change from BL)	16.03	1.98
	SD	± 80.975	± 93.884
	Composite Sleep Disturbance Index (CSDI) score (change from BL)	-2.4	-1.7
	SD	± 2.94	± 3.17

	Children's Global Assessment Scale (CGAS) score (change from BL)	2.1	1.4
	SD	± 8.55	± 12.12
	Strength and Difficulties Questionnaire (SDQ) total score (change from BL)	-0.8	0.2
	SD	± 3.21	± 2.53
	Caregivers' daytime sleepiness (ESS) (change from BL)	-0.7	+0.3
	SD	3.98	4.12
	Caregivers' well-being (WHO-5) (change from BL)	1.3	-0.5
	SD	4.96	4.27
	Caregivers' quality of sleep at night (PSQI) (change from BL)	-1.0	-0.5
	SD	3.01	3.13
Effect estimate per comparison	**Total sleep time** (min)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	32.43
		95% CI	(2.48, 62.38)
		P-value	0.034
	Sleep latency (min)	Comparison groups	Slenyto vs placebo

		Estimated treatment difference	-25.30
		95% CI	[-44.71,-5.90]
		P-value	0.011
	Wake time after sleep onset (min)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	0.08
		95% CI	[-7.02, 6.86]
		P-value	0.981
	Number of awakenings per night	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	-0.09
		95% CI	[-0.35, 0.16]
		P-value	0.474.
	Longest sleep period (min)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	42.16
		95% CI	[-0.42, 84.73]
		P-value	p=0.052
	Total time in bed per night (min)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	4.75
		95% CI	[-20.80, 30.29]
		P-value	0.713
	Composite Sleep Disturbance Index (CSDI) score	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	-0.92
		95% CI	[-1.93, 0.09]

		P-value	p=0.074
	Children's Global Assessment Scale (CGAS) score	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	0.13
		95% CI	[-3.64, 3.89]
		P-value	p=0.948
	Strength and Difficulties Questionnaire (SDQ)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	-1.01
		95% CI	[-2.12, 0.11]
		P-value	p=0.077
	Caregivers' daytime sleepiness (ESS)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	-1.29 points [-2.78, 0.20]
		95% CI	<variability>
		P-value	p=0.089
	Caregivers' well-being (WHO-5)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	2.17 points [0.53, 3.82]
		95% CI	<variability>
		P-value	P=0.01
	Caregivers' quality of sleep at night (PSQI)	Comparison groups	Slenyto vs placebo
		Estimated treatment difference	-0.81 [-1.97, 0.34]
		95% CI	<variability>
		P-value	P=0.166

Table Multiple imputation and baseline observation carried forward analyses of Sleep and Nap Diary variables

Variable		MMRM analysis (FAS)	Multiple imputation	BOCF
TST (minutes)	Treatment difference (SE)	32.43 (15.107)	33.11 (14.856)	32.57 (15.563)
	95% CI	2.48, 62.38	3.99, 62.23	1.68, 63.46
	p-value	0.034	0.026	0.039
Sleep latency (minutes)	Treatment difference (SE)	-25.30 (9.788)	-25.31 (10.022)	-23.09 (10.080)
	95% CI	-44.71, -5.90	-44.95, -5.67	-43.10, -3.09
	p-value	0.011	0.012	0.024
Duration of wake time (minutes)	Treatment difference (SE)	-0.08 (3.489)	-0.19 (3.156)	-0.19 (3.499)
	95% CI	-7.02, 6.86	-6.38, 5.99	-6.77, 7.15
	p-value	0.981	0.952	0.957
Number of awakenings	Treatment difference (SE)	-0.09 (0.129)	-0.08 (0.134)	-0.14 (0.131)
	95% CI	-0.35, 0.16	-0.35, 0.18	-0.40, 0.12
	p-value	0.474	0.531	0.286
Longest sleep duration (minutes)	Treatment difference (SE)	42.16 (21.440)	43.20 (20.878)	44.72 (21.856)
	95% CI	-0.42, 84.73	2.28, 84.12	1.29, 88.15
	p-value	0.052	0.039	0.044

BOCF = baseline observation carried forward; CI = confidence interval; FAS = full analysis set; MMRM = mixed-effects model for repeated-measures; SE = standard error; TST = total sleep time
Data source: Tables 14.2.1.4, 14.2.1.7, 14.2.1.10, 14.2.1.13, 14.2.1.16, and 14.2.14.1-10

Efficacy results from the initial 39 weeks of the open label extension period

Subjects (51 from the Slenyto and 44 from the placebo group, mean age 9 $\pm$ 4.24 years, range 2-17.0 years, 74.7% males) entered the open-label phase and 79 patients completed the 39 weeks follow-up period: 41 (Slenyto group) had 52 weeks and 38 (placebo group) had 39 weeks of continuous Slenyto treatment. The improvements in total sleep time (TST), sleep latency (SL) and duration of uninterrupted sleep (LSE; longest sleep episode) seen in the double blind-phase were maintained or enhanced throughout the follow up period. Subjects treated continuously with Slenyto for 52 weeks (N=41) slept on average (adjusted mean (SE)) 62.08 (21.5) minutes longer (p=0.007), fell asleep -48.6(10.2) minutes faster (p<0.001) and had longer uninterrupted sleep duration (89.1(25.5) minutes; p=0.001). In addition, quality of sleep improved (0.91 (0.22); p<0.001) and number of awakenings decreased > 50% from 0.78 to 0.3 (-0.41 (0.12) p=0.001).

Subjects initially randomized to placebo (N=38) also improved with Slenyto; improvements did not differ significantly between the randomization groups allowing to combine the groups in the follow up period regardless of randomization history. Altogether, by the end of the follow-up period, 55 (76%) of the 72 completers who provided SND data, achieved an overall improvement of one hour or more in TST, SL or both, over baseline with 2,5 or 10 mg/day (average daily dose of 5.3 mg). Decreases in CSDI sleep disturbance scores observed in the double blind phase were enhanced during the follow up period. After continuous 52 weeks of

treatment (N=41), mean (± SE) total CSDI score improved (decreased) -3.45(0.53) units from baseline on average (p<0.001) There was no evidence of decreased effectiveness of Slenyto over time.

Table 5: Sleep variables after 13, 26 and 39 weeks of open label Slenyto treatment of the study population*

Variable	13 weeks open label	26 weeks open label	39 weeks open label
TST (minutes)			
Estimated change from baseline (SE)	37.01 (10.263)	40.75 (12.344)	44.35 (13.935)
p-value	0.001	0.001	0.002
Sleep latency (minutes)			
Estimated change from baseline (SE)	-28.39 (5.678)	-41.9 (6.34)	-41.36 (6.64)
p-value	<0.001	<0.001	0.009
Number of awakenings			
Estimated change from baseline (SE)	-0.35 (0.080)	-0.38 (0.086)	-0.39 (0.096)
p-value	<0.001	<0.001	<0.001
Longest sleep duration (minutes)			
Estimated change from baseline (SE)	64.21 (12.576)	76.0 (15.5)	78.63 (17.18)
p-value	<0.001	<0.001	<0.001
Quality of Sleep			
Estimated change from baseline (SE)	0.53(0.103)	0.67(0.118)	0.72(0.135)
P-value	<0.001	<0.001	<0.001
Sleep Disturbance (CSDI)			
Estimated change from baseline (SE)	-2.46 (0.330)	-3.12(0.342)	-3.27(0.350)
P-value	<0.001	<0.001	<0.001

Source: Tables 14.2.6.3, 14.2.6.6, 14.2.6.15, 14.2.6.26 , 14.2.6.12, 14.2.7.3

*Patients in the Slenyto- randomised group had altogether 52 weeks and those in the placebo group had 39 weeks of continuous Slenyto treatment by the end of the 39 weeks open-label period

For the long term part, the effects by final dose after 26 weeks and 52 weeks of treatment are presented below. At week 52, 16 patients were on the 2 mg dose, 26 on the 5 mg dose, and 30 on the 10 mg dose.

Table 6 SND sleep variables by final dose

Variable	Group	N	Mean Change from Baseline (SE) 26 weeks	N	Mean Change from Baseline (SE) 52 weeks
2 mg Slenyto					
TST	Slenyto	32	56.88 (19.02)	16	94.91(29.03)
SL	Slenyto	32	-40.39(9.62)	16	-63.39(14.2)
LSD	Slenyto	27	61.11(19.87)	13	119.96 (31.31)
5 mg Slenyto population					
TST	Slenyto	59	26.24(11.89)	26	39.80(23.29)
SL	Slenyto	59	-21.88 (6.94)	26	-39.56(6.75)
LSD	Slenyto	56	65.71(16.1)	23	95.22 (32.05)
10 mg Ped PRM population					
TST	Slenyto			30	21.34(20.9)
SL	Slenyto			30	-31.17(12.54)
LSD	Slenyto			29	46.95 (24.75)
1**0 mg Slenyto subpopulation--**No further dose escalation needed					
TST	Slenyto			13/30	119.07 (28.7)

SL	Slenyto		13/30	-74.24 (19.13)

For the 10 mg treated group at week 52, 43.3% (13 of 30) improved by 60 minutes or more in mean TST and/or SL and did not need further dose escalation. The improvement in TST and SL in these participants was similar to those who reached their appropriate dose with 2-mg and 5-mg Slenyto. The rest (17 patients, comprising 23.6% of the total population) did not reach this milestone.

Treatment effects per age subgroup

Table 7 SND total sleep time change from baseline at 13 weeks DB MMRM analysis including Age as a factor FAS Set

Age	Slenyto (N=58) Adjusted Treatment Means (SE)	Placebo (N=61) Adjusted Treatment Means (SE)	Treatment Difference (SE)	P value
2-3 (N=14)	75.0 (45.45)	-14.17 (20.16)	89.17 (-9.95; 188.29)	0.07*
2-5 (N=33)	43.84(21.25)	25.45(20.20)	18.39(29.37)	0.533
6-12 (N=47)	62.82(16.87)	11.61(17.76)	51.21(24.50)	0.039
12-17 (N=39)	42.91(17.98)	19.82 (19.18)	23.09(26.19)	0.380

Source Table 14.2.14.13.1 *2 tailed t-test

Age groups according to Statistical Analysis Plan 10 Oct 2016

The applicant also looked at the responses according to age groups at week 52 by dividing the ages into three groups that are more or less similar in sample size and adding now the very young age group of 2-3 years old separately:

• 2-3 year olds - to look at the very young children that might be not officially diagnosed yet but showing trait of autism,

• 2-7 year olds - as it was important to look at this age group as these ages were not included in the PK study,

• 8-11 year olds - as these are still pre-pubertal children but were included also in the PK study, and

• adolescents – 12 years old and above.

Table 8 Mean change from baseline in SND TST and SL by age - Week 52

Age range	N	Mean dose (range)	Mean change in TST (SE)	Mean change in SL (SE)
2-3	11	5.23 (2/5/10)	38.84 (46.77)	-44.56 (10.38)
2-7	28	5.64 (2/5/10)	52.36 (26.52)	-48.66 (8.87)
8-11	20	5.20 (2/5/10)	45.12 (26.46)	-41.89 (12.31)
12-18	24	8.33 (2/5/10)	34.37 (18.58)	-32.40 (13.80)

Long term effects on caregivers [Malow et al draft pre-submission, Maras et al, submitted for publication February 2018].

By the end of the 39 weeks open label follow up period, caregivers of children treated continuously with Slenyto for 52 weeks (N=41) had significant improvements in sleep quality (mean(SE) change from baseline in PSQI score -2.20 (0.517) units; p<0.001) , well-being (mean(SE) change from baseline in WHO-5 2.41(0.836) units, p=0.006, and CSDI assessed satisfaction of their child's sleep patterns 1.95(0.218, p<0.001).

Subjects initially randomized to placebo (N=38) also improved with Slenyto; improvements did not differ significantly between the randomization groups allowing to combine the groups in the follow up period regardless of randomization history. There was a gradual improvement in PSQI over time and by the end of the follow up period mean PSQI score of the caregivers was lower (improved) by 1.79(0.42) units compared to baseline (p<0.001).

In addition, caregivers well-being improved significantly with Slenyto treatment and by the end of the 39 weeks follow up period, mean(SE) WHO-5 increased (improved) units compared to baseline (1.96(0.59) p=0.001).

Importantly, parents satisfaction of their Child's sleep increased (CSDI) significantly and by the end of the follow up period it was improved by mean (SE) 1.9(0.15) units on a scale of 1-5 (p<0.001).

Daytime sleepiness (ESS) tended to improve as well and by the end of the 39 weeks follow up period, mean(SE) score decreased -0.89 (0.500) units (p=0.078).

Supportive data

Publications on the effects of melatonin on the sleep problems in certain neurogenetic diseases

De Leersnyder et al, 2003 showed that Circadin 6 mg markedly improved sleep disturbances in 10 SMS children. Before drug administration, mean sleep onset was 9:15 pm (range 8:30-10 pm), mean waking time was 5:40 am (range 4 -7 am), and mean duration of sleep was 8.20 (range 7.15-9) hours. Children were given beta blockers during daytime to block the endogenous production of melatonin, which is abnormally timed to the daytime in these children, and Circadin at night to replenish the nocturnal melatonin. Night parameters dramatically improved in children under this regimen. Mean sleep onset was delayed to 9:45 pm (range 9-11 pm), mean waking delayed to 6:40 am (range 6-8 am), and mean duration of sleep extended to 8.50 hours (range 8-9.30 hours). Children did not wake up during the night and EEG recordings confirmed a more regular sleep stage organisation and a rapid access to sleep stage 3-4 (slow wave stage). Sleep was deep and quiet for both children and their family and day/night life was dramatically improved.

De Leersnyder et al, 2011: The long-term effectiveness and safety of Circadin treatment dose range 4-6 mg, were assessed in 88 children (42 girls and 46 boys) with neurodevelopmental disorders. These patients participated in a compassionate-use program with the drug Circadin (2 mg) in France, and received treatment in the context of regular care by a specialized physician. The population consisted of: **Smith-Magenis syndrome** (47 patients), mental retardation (14 patients), encephalopathy (seven patients), autism (seven patients), **Angelman syndrome** (five patients), **Rett syndrome** (five patients), **Bourneville syndrome** (one patient), blindness (one patient), and delayed sleep-phase syndrome (one patient). Within 3 months, sleep latency with Circadin decreased by 44.0% (P < 0.001), sleep duration increased by 10.1% (P < 0.001), the

number of awakenings decreased by 75% (P < 0.001), and sleep quality improved by 75%, compared with baseline (P < 0.001).

Braam et al 2008 performed a randomized placebo-controlled open-label study in 8 children with **Angelman syndrome** with chronic insomnia. Patients received, depending on age, either melatonin (N=4, immediate release) 5 mg (≥6 years) or 2.5 mg (<6 years), or placebo (N=4), followed by 4 weeks of open treatment. Parents recorded lights off time, sleep onset time, wake-up time, and epileptic seizures in a diary. Salivary melatonin levels were measured at baseline and the last evening of the fourth treatment week. Melatonin significantly advanced sleep onset by 28 minutes, decreased sleep latency by 32 minutes, increased total sleep time by 56 minutes, reduced the number of nights with wakes from 3.1 to 1.6 nights a week, and increased endogenous salivary melatonin levels.

Zhdanova et al, 1999 treated 13 **Angelman syndrome** children suffering from insomnia with 0.3 mg dose of melatonin administered daily 0.5-1 hour before habitual bedtime. They reported on a significant decrease in motor activity during the sleep period and an increase in the duration of the total sleep period.

O'Callaghan et al, 1999 reported on the use of melatonin to treat sleep disorders in **tuberous sclerosis**. This was a randomized double-blind placebo-controlled crossover study on 7 patients aged 2 to 28 years (median age 11 years) with confirmed diagnoses of tuberous sclerosis and significant sleep disorder. All patients had epilepsy and learning difficulties. The initial treatment period of 2 weeks was followed by a 1-week wash-out period before patients were crossed over to the alternate therapy for a further 2 weeks. Patients treated with melatonin (5 mg, immediate release, 20 min before bedtime) had a mean improvement in total sleep time of 33 minutes (95% CI, 0.088 to 1.01 P=0.027). The mean sleep-onset time decreased by 23.4 min with a tendency to benefit in favour of melatonin (P=0.079). There was no obvious trend in this group towards improvement in the mean number of awakenings per night.

McArthur and Budden, 1998: nine girls with **Rett syndrome** underwent a 4-week melatonin treatment period in a double blind placebo controlled crossover study with one week washout between phases. Immediate release Melatonin with doses ranging from 2.5 mg – 7.5 mg based upon body weights, given orally or via gastrostomy, significantly decreased SL ($p<0.05$). TST improvement was seen in patients with the worse baseline sleep quality.

Altogether, it seems that children with certain neurogenetic disorders and insomnia similarly respond to melatonin and no safety issues are evident.

Use of Circadin in the target population in France under RTU

In July 2015, the National Agency for the Safety of Medicines (ANSM) issued a unanimous positive advice on the set up of RTU (temporary registration use) 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), Autism spectrum disorders

The recommended posology of Circadin is 4 to 6 mg per day;

Patients follow up according to protocol + electronic portal;

RTU is valid for a duration of three years which can be renewed.

Up till February 2018 – 306 physicians registered and 435 patients included in the program:

- 373 Autism Spectrum Disorders
- 16 Smith Magenis Syndrome
- 7 Angelman Syndrome
- 9 Rett syndrome
- 2 TSB syndrome
- 28 Others (ADHD, Fetal Alcohol Syndrome (FAS), Cornelia de Lange syndrome and unknown)

2.9.1. Discussion on clinical efficacy

The pivotal trial

Overall, eligibility criteria in the pivotal trial are considered adequate. However, it is noted that a 4-week basic sleep hygiene and behavioural intervention period was included between screening and randomisation for children who did not have a documented history of such interventions. Sleep hygiene interventions are always recommended before escalating to pharmacological treatment of sleep disturbances in children. Thus, Slenyto is only indicated in children who did not have a sufficient response to sleep hygiene and behavioural interventions, which is included in the SmPC indication text.

It is also noted that ADHD was a common concomitant disorder to ASD in this study (28.8%) and that ongoing treatment with stimulants was allowed. It is also important that children on stable medication with β-blockers took these in the morning, and not in the evening, since β-blockers may reduce endogenous melatonin levels and thus might cause disturbed sleep..

Discontinuation rates were generally low, and it was noted that more patients in the placebo group discontinued treatment than in the Slenyto group. It is noted that all patients who entered the open-label phase of the study also completed this part of the study.

Concomitant medications taken reported as protocol deviations mostly reflect the pattern of concomitant medications taken in this patient population, and thus the protocol may have been too strict on this matter. It is actually an advantage of the study that the concomitant medications reflect the real-life situation.

The inclusion criteria in the child efficacy study allowed subjects between 2 and 17.5 years to be included into the study. It is noted that the age span was indeed 2-17 years. 35.2% of the patients were aged 2-6 years, 45,6% aged 7-12 and the remaining 21./% were aged 13-17 years. The efficacy and safety results in these three subgroups based on age appear similar. However, since the children younger than 7 were not included in the PK study and the non-clinical juvenile study was performed in rats corresponding to a lower limit of age of 3-4 years, the number of children at each age is important. The study population included 29 children aged 2-6 years (3 were 2 years old, 10 were 3 years old, 7 were 4 years old, 6 were 5 years old and 3 were 6 years old out of the 95 patients completing the 6 months period. All of these children had a definitive diagnosis of ASD or neurogenetic disorders before entering the study. Even though ASD can be diagnosed as early as 2 years of age,

according to the CDC Centers for Disease Control and Prevention survey on Autism Spectrum Disorder (ASD) (CDC 2018), the median age of first ASD diagnosis of Autistic disorder is 3 years and 10 months, of ASD/pervasive developmental disorder (PDD) is 4 years and 8 months. The average age of ASD diagnosis may vary by country and region depending on information about autism among doctors of the first contact (paediatricians and GPs), parents' awareness and accessibility of specialists services (Ferrante et al, 2015; Jo et al, 2015).

According to the inclusion criteria, in addition to ASD, patients with Smith-Magenis Syndrome, Angelman or Bourneville's disease (Tuberous sclerosis) were to be included into the study. However, only 4 patients with Smith-Magenis Syndrome and no patients with Angelman or Bourneville's disease (Tuberous sclerosis) were included. This means that it is hard to draw any specific conclusions from the results of this study on efficacy of melatonin in these rare neurogenetic syndromes.

Since Slenyto is a prolonged release formulation, the plasma concentration curve during the night is supposed to mimic that of the natural hormone secretion of melatonin. Thus, logically, Slenyto would be expected to demonstrate a positive treatment effect on both sleep onset difficulties, as measured by sleep (onset) latency, as well as sleep maintenance parameters such as total sleep time, number of awakenings, and wake time during night. However, although it is recognised that Slenyto does induce positive effects on both sleep latency and total sleep time, it doesn't significantly improve neither number of awakenings nor wake time during night. The sleep diary kept by the parents could be insensitive to the two latter parameters. The applicant was aiming to use wrist-worn actigraphs to capture sleep-related data automatically during the pivotal study, but due to insensitivity of the actigraphs to awakenings during the night and the well-known fact that children with ASD don't easily accept a change of routines such as wearing a wrist-worn actigraph, this was not feasibly and didn't yield any useful data.

The EMA guideline on insomnia mentions that the following clinical efficacy criteria should be evaluated as a minimum acceptable standard: sleep onset latency; sleep continuity; sleep duration; feeling of restorative sleep and quality of sleep; subsequent daytime functioning in the natural setting. Ideally, all these aspects will be improved by treatment with a given medicinal product in the phase three programme. It is recognised that improvement in individual criteria may be important for particular subgroups of patients, but if only one aspect of insomnia (e.g. difficulty falling asleep or difficulty maintaining sleep) is improved, the clinical relevance of these effects may be difficult to establish. In such cases the demonstrated effects should be based on a clear understanding of the underlying mechanism of action, should be robust and consistent and be supported by improvement in quality of day time functioning (mandatory as a co-primary endpoint). In this context, the additional measurement of sleep architecture by multichannel polysomnography is considered helpful for phase three studies.

Thus, according to the EMA guidelines on insomnia, effects on sleep latency or maintenance of sleep should be supported by improvement in quality of day time functioning, which is considered mandatory as a co-primary endpoint. In these children, among a number of outcomes on day-time functioning, only the subdomain "Externalizing behaviours" of SDQ, was significantly positively affected in these children, which should be considered a clear short-coming of this study. It could however be acknowledged that day-time functioning or quality of life cannot be assessed by the subjects themselves as in adult insomnia studies and day-time functioning tests may not be sensitive enough to capture any changes in these children. The improved well-being of the parents, also being recognised as a secondary endpoint in the section on paediatric trials of the EMA insomnia guideline, offers some support to the notion that Slenyto has beneficial effects in these children. Since younger children with ASD require supervision by their parents/caregivers, the impact of disturbed sleep

including awakenings in children with ASD almost always leads to a disturbed sleep of their parents, secondarily affecting their day-time functioning and well-being.

The use of MMRM for the primary analysis was initially not fully endorsed, since it mimics a completers' analysis and relies on the unverifiable assumption that missing data are missing at random. However, sensitivity analysis using alternative methods to handle missing data (MI and BOCF) confirmed the results of the primary analysis and it is concluded that the MMRM results should be used in the SmPC.

The significant effects on the primary endpoint total sleep time and the secondary endpoint sleep latency seemed stable over the duration of the study with an effect appearing already after 3 weeks' treatment and apparently maintained through the 13 weeks' of open label treatment.

The well-being of the caregivers, i.e. the parents, could actually be considered an important endpoint for this patient population of children with ASD which often impose a great burden on the caregivers. Therefore, it is noted that there was a trend for improvement in daytime sleepiness of the caregivers during the double-blind period and a significant improvement in the caregivers' well-being, as measured by WHO-5. The caregivers' quality of sleep at night was not significantly affected, which may not be so surprising, given the fact that the number of awakenings or wake time during night was not significantly affected in the children.

It appears that, for the children who had a satisfying effect on TST and sleep latency at the 2 mg dose, positive treatment effects were maintained during both the double blind and open label study periods. For children requiring a dose increase to the 5 mg dose, the effects on TST and sleep latency increased, but were still inferior in comparison to the 2 mg dose, both during the double blind period and also after 13 weeks' open label treatment. This might indicate that some children need a higher dose than 5 mg to get optimal treatment effects on TST and sleep latency. Indeed, after the initial 13 weeks' treatment period in the open label phase of the study, a dose titration from 5 mg to 10 mg was allowed.

On the other hand, the 5 mg dose gave a better response on number of awakenings and wake time than the 2 mg dose, which might indicate that a higher dose (i.e. 5 mg) at bedtime leads to higher persistent exposure of melatonin during the later hours of night thus preventing awakenings.

The proposed posology section of the SmPC recommends an initial dose of 2 mg, which could be up-titrated to 5 mg after 3 weeks of treatment in case of an inadequate response. This is in line with the experience from the pivotal trial. In addition, the trial allowed a further dose escalation to 10 mg for the extension study period following the initial 13 weeks of the open label trial. At week 52, 16 patients were on the 2 mg dose, 26 on the 5 mg dose, and 30 on the 10 mg dose. The results for the three different doses after 52 weeks' treatment showed that the inverse dose-dependent effect on TST and SL, with the 2 mg dose was having the greatest changes from baseline and the 10 mg dose having the smallest effects. This might be related to the dose escalation, i.e. patients being non-responders in terms of TST and SL were up-titrated to the next higher dose until they reached the 10 mg dose.

To better understand the clinical benefit in patients given the 10 mg dose, the Applicant looked at all patients with clinically relevant improvements in either TST (45 minutes and more), SL (15 minutes and over) or both (altogether 19 of the 30 patients treated) receiving this dose at week 52, as they anticipated that this group might be considered by the physician as clinically responding to the drug and would continue to use the drug in the clinical setting.

Table 9 SND TST and SL in patients who were on the 10 mg dose at week 52 and showed clinically relevant improvement in TST, SL or both

Variable	Mean (SE) Change from BL minutes		
	Slenyto 5 mg week 26	Slenyto 10 mg week 52	P value between weeks 26 and 52* (N)
TST	45.71 (19.7)	62.35 (28.01)	P=0.31 (N=19)
SL	-40.43(12.58)	-65.15(13.65)	P=0.006(N=19)

*Paired t-test

It can be seen that these patients showed improvement on the 5 mg dose (by a mean of 45.71 minutes on TST and -40.43 minutes on SL) but received further benefit on the 10 mg dose, with additional mean improvement of 16.63 minutes in TST and -24.72 minutes in SL (p=0.006). The number of patients attaining a clinically relevant response also increased with the 10 mg dose (Table 6). It can be seen clearly that escalating the dose to 10 mg in this patient group increased the number of patients responding to the treatment and despite the low sample size, the increase was statistically significant for SL (p=0.003).

Table 10 SND TST and SL response rate after 26 weeks on 5 mg and after 52 weeks on 10 mg

Variable (N)	%Responders*		
	Slenyto 5 mg week 26	Slenyto 10 mg week 52	P value between weeks 26 and 52 (N)
TST	42.1%	52.6%	P=0.52 (N=19)
SL	52.6%	94.7%	P=0.003 (N=19)

*TST responder: A patient is defined as a TST responder if the change from baseline in mean TST is 45 minutes or greater (increase in TST) over the 14 days prior to each scheduled visit. Sleep latency responder: A patient is defined as a sleep latency responder if the change from baseline in mean sleep latency is 15 minutes or greater (reduction in sleep latency) over the 14 days prior to each scheduled visit.

However, there may be many patients among these which are actually true non-responders to any dose of melatonin, which emphasizes the need for a stopping rule related to insufficient efficacy. The applicant has provided stopping rule for the SmPC guiding the treating physician on when to evaluate whether there is a relevant treatment effect or if treatment should be discontinued due to lack of efficacy. An example could be: "After a relevant treatment period, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. However, since cases of lost effect after dose titration to a higher dose have been described, possibly related to the patients being slow CYP1A2 metabolisers, the following instruction was included in the posology section of the SmPC: "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."

There is also experience in society from the use of higher doses than 5 mg, since melatonin has been used extensively the last decade as an off-label treatment for children with neurodevelopmental disorders with reported doses within the 2-10 mg range. For example, a recent prospective observational study on 45 children with neurodevelopmental disorders (probably using an IR formulation) reported that 38% of children responded to low (2.5-3 mg), 31% to medium (5-6 mg) and 9% to high doses (9-10 mg) of melatonin, with a significant increase in total hours of sleep/night, decreased sleep onset delay and decreased number of awakenings/night (all: p = 0.001), as measured with sleep diaries (Ayyash et al., 2015: Expert Rev Neurother. 2015;15(6):711-7).

At week 13 of the open-label phase, 30 of the patients on the 5 mg dose were dose-increased to 10 mg. The applicant has chosen to only look at the patients treated at the 10 mg dose and with clinically relevant improvements in either TST (45 minutes and more), SL (15 minutes and over) or both (altogether 19 of the 30 patients treated) receiving this dose at week 52, as they anticipated that this group might be considered by the physician as clinically responding to the drug and would continue to use the drug in the clinical setting. Thus,

only 19/30 (63.3%) of the patients treated at 10 mg are included in the analysis. The assessor interprets this as indicating that around 37% of the patients dose-escalating up to the highest dose (10 mg) didn't receive clinical benefit from this dose. At week 52, 16 patients were on the 2 mg dose, 26 on the 5 mg dose, and 30 on the 10 mg dose out of the 72 that had SND data. Thus 30/72 had been dose-escalated up to 10 mg, of which 19/30 had clinical benefit.

The 10 mg dose can be accepted as part of the posology, since 19/30 (63.3%) of the children not having a clinically relevant effect at the 5 mg dose responded to the 10 mg dose. However, the prescriber should consider a down-titration from a higher dose before discontinuing treatment due to lack of efficacy, in case the effect is lower at this dose than at the next lower dose, since there are described cases in the literature who are slow CYP 1A2 metabolisers and may get extensively high melatonin levels if treated at higher doses.

The applicant has presented a review of publications on treatment with melatonin in children with these neurogenetic diseases and sleep problems. In particular, patients with Smith-Magenis syndrome have an abnormal melatonin circadian rhythm and have been reported to benefit from melatonin treatment. For Smith-Magenis syndrome, an inverse diurnal melatonin secretion curve has been shown and sleep problems are central in the symptoms of the disorder with daytime sleepiness and disturbed sleep during the night with night-time awakenings. For Angelman syndrome, the applicant stated that sleep disturbances are included in the diagnostic criteria, but according the cited reference, sleep disturbance is only an associated clinical characteristic of the disease, occurring in 20-80% of the patients (Williams et al., Angelman syndrome: Consensus for diagnostic criteria, Am J Med genetics 56:237-238 (1995)). In addition, in the Braam et al publication (J Child Neurol, 23(6), pp 649-654, 2008) it was noted that salivary melatonin levels were extremely high in 3 out of 4 children receiving melatonin and the authors found it likely that this was caused by a low activity of CYP1A2 in these children, which would implicate that children with Angelman should need lower doses of melatonin than others. For Rett syndrome, Tuberous sclerosis and Williams syndrome, the data on sleep problems are more scarce.

2.9.2. Conclusions on clinical efficacy

The magnitude of the favourable effects of Slenyto 2- 10 mg on sleep latency and total sleep time in the pivotal study in patients with ASD, are considered to be of clinical relevance even though it is noted that not all secondary endpoints, including number of awakenings and various other assessments scales on daytime function of the children and caregivers' sleep, were positively affected. The improved sleep endpoints in the children and well-being of the parents are however considered important to the well-being of the child with ASD and the caregivers. In addition, some literature data indicate that children with neurodevelopmental disorders might suffer from low endogenous melatonin secretion and abnormal circadian rhythmicity which may support the documented effect in the pivotal study. This biological rationale also seems to be documented for children with Smith-Magenis Syndrome while the data are more uncertain for the other neurogenetic disorders proposed to be included in the therapeutic indication by the Applicant (Angelman or Bourneville's disease (Tuberous sclerosis)). For Smith-Magenis syndrome, an inverted melatonin diurnal secretion curve has been demonstrated and there is both data from the present study and publications on similar efficacy levels in these children as in children with ASD.

The CHMP concluded that the available data from the clinical study and literature confirms the efficacy of Slenyto in the approved indication.

2.10. Clinical safety

Melatonin has been administered to humans in numerous studies employing a wide range of doses and for short to long-term periods (1 day to 18 months). Eighty-one studies were reviewed for adverse events (AEs) as a consequence of a literature search conducted on all published human melatonin studies (Zisapel, 1999). The objective of the review was to identify any AEs events experienced by subjects as a result of the external administration of melatonin. Thus, only studies of the exogenous effects of melatonin administration in human subjects were included in the review. Fifty-eight of the 81 studies identified in the literature search met this criterion. The studies reviewed were not necessarily sleep related. Some of the publications identified were abstracts, letters, or review papers. Only 6 papers out of 58 (10.3%) reported any adverse experiences (Zisapel, 1999). In addition, data from published studies also supports the tolerability and safety of melatonin treatment for periods up to 6 years with doses up to 300 mg, which is far in excess of the proposed dose. Overall AEs following melatonin use have been documented in a number of reports, as discussed below.

Melatonin has also been marketed at doses ranging from 0.5 to 80 mg as an oral food supplement in the United States for many years and as such falls under the FDA's Dietary Supplement Health and Education Act (DSHEA) category of "other dietary substance". The in depth evaluation of the literature data on the safety of melatonin became available in April, 2004 when the Committee on the Framework for Evaluating the Safety of Dietary Supplements of the National Academies announced the publication of a report entitled "Dietary Supplements: A Framework for Evaluating Safety". The report contains numerous references to melatonin and includes an 84-page prototype melatonin monograph. Conclusions and recommendations about the safety of the ingredient based on the strength of the scientific evidence were that short-term use of melatonin in a daily amount of 10 mg or less does not raise concern of harm for healthy adults who are not taking concurrent medications or other dietary supplements (Prototype monograph on melatonin 2004).

Patient exposure

Circadin was administered to humans in numerous studies employing a wide range of doses and for short to long-term periods (1 day to 18 months). Out of a total of 3194 adult patients who received Circadin for different periods in all Neurim studies and other studies, 2583 were treated in Neurim sponsored trials, 1850 of them in the Good Clinical Practice (GCP) studies (studies 30424, I, IV, V, VII, VIII, IX and 112006), and the remainder in special population studies (951004, 951003, 961009, NEU BP) and the post marketing surveillance study 12545A (Hajak et al, 2014). These studies had data on length of exposure, enabling an adjustment of AE incidence rates for differences in length of exposure.

In the adult Circadin studies, 794 subjects have been treated for 6 months and 146 subjects for 1 year or longer.

Two clinical studies have been conducted to date with Slenyto tablets of the dose strength 1 mg (the paediatric formulation of Circadin). In the paediatric Circadin studies, a total of 118 children have been treated.

During the double-blind phase (13 weeks), mean time on treatment was 89.1 days in the Slenyto group (range 14 to 149 days) compared to 77.7 days in the placebo group (range 15 to 112 days). During the open-label phase (91 weeks), mean time on treatment was 517.8 days in the Slenyto/Slenyto group (range 3 to 666 days) and 545.5 days in the Placebo/Slenyto group (range 80 to 659 days). For patients who received Slenyto in both the double-blind phase and during the open-label phase, mean total time on Slenyto treatment across both phases was 547.4 days (range 14 to 770 days).

Adverse events

In adults

Of a total of 3194 adult patients who received Circadin for different periods in all Neurim studies and other studies, 2583 were treated in Neurim studies. Of these, 1850 were treated in studies 30424, I, IV, V, VII, VIII, IX and 112006 for which a pooled analysis was conducted. These controlled clinical studies had data on length of exposure thus enabling an adjustment of AE incidence rates for differences of length of exposure. It can be concluded from this pooled Circadin AE summary in adults that no significant Circadin induced AEs were found compared to placebo. On the contrary, the rate of patients with AEs per 100 patient weeks of therapy was higher in the placebo group (5.743) than the Circadin group (3.013).

Appendix 2 describes common AEs for Circadin and placebo treated adult patients in the pooled analysis. The most common AEs were headache, nasopharyngitis, back pain, and arthralgia, which were common by Medical Dictionary for Regulatory Activities (MedDRA) definition (>1/100, <1/10), in both the Circadin and placebo treated groups. However, these AEs were not necessarily related to treatment.

In children

In the PK study CHDR1219, AEs with a possible or probable relationship with administration of 2 and 10 mg Slenyto included fatigue (in 7 out of 16 patients after 2 mg dose and in 8 out of 16 patients after 10 mg dose), sensation of heaviness (1 out of 16 after 2 mg), somnolence (3 out of 16 after 2 mg; 2 out of 16 after 10 mg), falling asleep (2 out of 16 after both 2 and 10 mg), headache (1 out of 16 after 2 mg; 3 out of 16 after 10 mg), and nausea (1 out of 16 after 10 mg). All AEs were transient and mild. Nausea, fatigue and headache were more frequently reported following Slenyto 10 mg compared with Slenyto 2 mg.

In the efficacy and safety study NEU_CH_7911, treatment-emergent AEs (TEAEs) during the double-blind phase were reported by 51 (85.0%) patients in the Slenyto group (202 events) and by 50 (76.9%) patients in the placebo group (159 events). The most commonly reported TEAEs (reported by ≥10% of patients in any group) are summarised in the Table below. During the double-blind phase, the most commonly reported AEs were fatigue and somnolence. Somnolence and headache were both more common in the Slenyto group than in the placebo group.

During the open-label phase, the frequency of reported TEAEs was similar to that in the Slenyto-goup during the double-blind phase, with TEAEs reported by 80 (84.2%) patients during the open-label phase. The most commonly reported AEs in Slenyto-treated subjects were somnolence and fatigue in both the double-blind and open-label phases (Table below). Reporting rates for all AEs were similar between patients continuing Slenyto treatment from the double-blind phase and those switching from placebo to Slenyto for the open-label phase.

Table 11 Most commonly reported treatment-emergent adverse events (safety set)

	Double-blind phase				Open-label phase	
	Circadin®		Placebo		All Circadin®	
	Patients (N=60)	Events	Patients (N=65)	Events	Patients (N=95)	Event
Number of patients with at least one TEAE	51 (85.0%)		50 (76.9%)		80 (84.2%)	
Total number of AEs		208		156		524
Preferred term						
Somnolence	17 (28.3%)	18	8 (12.3%)	8	24 (25.3%)	31
Fatigue	15 (25.0%)	19	12 (18.5%)	13	25 (26.3%)	33
Mood swings	10 (16.7%)	10	11 (16.9%)	12	17 (17.9%)	24
Upper respiratory tract infection	9 (15.0%)	9	7 (10.8%)	8	14 (14.7%)	24
Vomiting	8 (13.3%)	11	10 (15.4%)	10	20 (21.1%)	33
Agitation	11 (18.3%)	12	7 (10.8%)	8	8 (8.4%)	10
Headache	8 (13.3%)	8	4 (6.2%)	4	12 (12.6%)	12
Cough	7 (11.7%)	7	5 (7.7%)	5	16 (16.8%)	27
Dyspnoea	6 (10.0%)	6	4 (6.2%)	4	10 (10.5%)	10
Rash	3 (5.0%)	3	3 (4.6%)	3	10 (10.5%)	10

AE = adverse event; TEAE = treatment-emergent adverse event This table includes AEs reported by ≥10% patients in any group. Data source: Tables 14.3.2.4 and 14.3.2.5.

Table 12 Most commonly reported treatment-related adverse events (safety set)

	Double-blind phase				Open-label phase	
	Circadin®		Placebo		All Circadin®	
	Patients (N=60)	Events	Patients (N=65)	Events	Patients (N=95)	Events
Number of patients with at least one treatment-related AE	12 (20.0%)		11 (16.9%)		8 (8.4%)	
Total number of AEs		28		17		13
Preferred term						
Somnolence	7 (11.7%)	7	2 (3.1%)	2	6 (6.3%)	6
Fatigue	2 (3.3%)	4	3 (4.6%)	3	6 (6.3%)	8
Mood swings	1 (1.7%)	1	4 (6.2%)	4	4 (4.2%)	4

AE = adverse event
This table includes AEs reported as treatment-related by ≥5% patients in any group.
Data source: Tables 14.3.2.8.1 and 14.3.2.9.1.

Serious adverse events and deaths

Deaths

There have been 3 deaths in the adult studies. Two deaths reported from Neurim IV were from two elderly patients, one male (87 years) with acute pulmonary oedema and one female (84 years) with myocardial infarction. Both events were considered not related to the study drug or improbably related by the investigator.

One death was reported in study Neurim 112006 for a patient receiving placebo, and was considered unrelated to study drug.

There were no deaths in either of the paediatric studies.

SAEs

There have been 61 serious adverse events (SAEs) reported in the adult studies (these include the 3 deaths described above that were all considered unrelated to the study drug). Out of the remaining 57 SAEs, 56 were considered not related to the study drug, or improbably related: 5 from Neurim IV, 9 from Neurim V, 2 from Neurim VII and 40 from Neurim 112006. One patient receiving Circadin in study Neurim 112006 had an SAE of palpitations during the extension period of that was considered drug-related. There were no SAEs reported in the post marketing surveillance study Neurim 12545A among a safety population of 652.

There were no SAEs in the paediatric PK study CHDR1219. In the efficacy and safety study NEU_CH_7911, 1 patient in the placebo group during double-blind phase was hospitalised for SAEs of pneumonia (mild) and respiratory tract infection viral (severe); both events were recorded as not related to study treatment. There were no SAEs in the Slenyto group during the double-blind phase. In the open-label phase, 6 patients experienced treatment-emergent SAEs:

• Patient in the Slenyto/Slenyto group was hospitalized for an SAE of aggression (severe; not related to study treatment).

• Patient in the Placebo/Slenyto group was hospitalized for an SAE of constipation (moderate; not related to study treatment).

• Patient in the Placebo/Slenyto group was hospitalized for an SAE of otitis media acute (moderate; not related to study treatment).

• Patient in the Placebo/Slenyto group was hospitalized for an SAE of lower respiratory tract infection (mild, unlikely related to study treatment).

• Patient in the Placebo/Slenyto group was hospitalized for an SAE of oppositional defiant disorder (severe, unlikely related to study treatment).

• Patient in the Placebo/Slenyto group was hospitalized for an SAE of eye infection (moderate, not related to study treatment).

AEs leading to discontinuation

In the Circadin group in the adult patient studies, there were 72 cases (2.9% of the safety population) of AEs leading to discontinuation of the patient. In the placebo group there were 462 cases (4.0% of the safety population) of AEs leading to discontinuation of the patient. Overall there was a higher percentage of discontinuation due to AEs in the placebo group than in the Circadin group, demonstrating the high safety profile of the drug. No specific symptoms were associated with withdrawal of patients in the Circadin vs placebo treatment.

There were no AEs leading to discontinuation in the paediatric PK study CHDR1219. In the double-blind phase of the efficacy and safety study NEU_CH_7911, one patient in the Slenyto group permanently discontinued study drug due to fatigue, agitation, and stereotypy (all non-serious AEs; all considered by the investigator as probably related to study treatment). One patient in the placebo group temporarily discontinued study drug due to pneumonia, respiratory tract infection viral (both SAEs) and tachypnoea (non-serious) while in hospital,

however, the patient continued in the study following hospitalisation. In the open-label phase, 8 patients discontinued study drug due to TEAEs:

• Patient in the Slenyto group discontinued study drug due to apathy, and fatigue (both non-serious, severe AEs and considered by the investigator as possibly related to study treatment).

• Patient in the Slenyto group discontinued study drug due to malaise (non-serious, mild AE and considered by the investigator to be unlikely related to study treatment).

• Patient in the Slenyto group discontinued study drug due to mood altered (nonserious, severe AE and considered by the investigator to be possibly related to study treatment).

• Patient in the Slenyto group discontinued study drug due to insomnia (non-serious, severe AE and considered by the investigator to be not related to study treatment).

• Patient in the Slenyto group discontinued study drug due to trichotillomania (nonserious, moderate AE and considered by the investigator to be not related to study treatment).

• Patient in the Slenyto group discontinued study drug due to headache (non-serious, severe AE and considered by the investigator to be possibly related to study treatment).

• Patient in the placebo group discontinued study drug due to head injury (non-serious, mild AE and considered by the investigator to be unlikely related to study treatment).

• Patient in the placebo group discontinued study drug due to sinusitis (non-serious, moderate AE and considered by the investigator to be not related to study treatment)

Laboratory findings

No significant melatonin induced changes in laboratory parameters were found in short-term (3 weeks) or long-term adult studies (up to 18 months).

Vital signs were not recorded in the paediatric PK study CHDR1219. In study NEU_CH_7911, vital signs were recorded at each visit, but there were no notable differences between Slenyto and placebo for mean changes in blood pressure, pulse rate, respiratory rate, or temperature.

Effects of Melatonin on Reproductive Physiology and the Hypothalamo-Pituitary-Gonadal-Adrenal Axes

There is no literature to suggest that exogenous melatonin, at doses similar to those of Circadin and Slenyto and even 25 times higher, affects the hypothalamo-pituitarygonadal- adrenal (HPA/HPG) pathways in ways other than those seen normally at night when melatonin is produced endogenously. Furthermore, the non-clinical studies do not show any evidence of effects on the HPA/HPG axis. Neurim's own data indicated that prolonged use (up to 18 months) of Circadin had no effect on the male endocrine system. The company sponsored a meta-analysis in an effort to reveal trends, if any, of the effects of melatonin on the HPA/HPG hormones (Schmidhauser 2004). This analysis consistently demonstrated that effects on hormonal levels, if any, were in line with the physiological activity of melatonin as a signal of darkness in the organism and in any case remained within normal limits under a variety of clinical conditions. The table below presents the ranges found for the major hormones of the HPA/HPG axes in control- and melatonin-treated subjects, and the respective normal adult ranges for these hormones. As can be seen, there is no evidence suggesting that exogenous melatonin, at doses similar to those of Circadin and Slenyto, and even 5-fold greater, affects the HPA/HPG pathways in ways other than mimicking those seen normally at night when melatonin is produced endogenously. Moreover, in

order to show any effects of melatonin on HPA/HPG pathways, melatonin has to be given at daytime, i.e. when it is not present endogenously, and even under those conditions it only demonstrates effects resembling the physiological changes that occur at night, both in nature and magnitude.

Table 13 Normal Ranges and Levels of HPA/HPG Axes Hormones in Melatonin and Placebo Treated subjects

Measured Hormone	Normal Range For Adult Females	Normal Range For Adult Males	Ranges in Melatonin-treated Subjects	Ranges in Placebo treated Subjects
Prolactin (ng/ mL)	1.8 – 29.2		10.26 – 26.9	8.0 – 12.5
		2.17 – 17.7	5.20 - 10.2	3.98 – 8.1
Luteinising hormone (U/L)	0.5 – 16.9		3.9 – 6.6	4.5 – 6.9
		1.5 – 34.6	2.6 - 12.9	2.4 – 10.8
Follicle stimulating hormone	1.5 – 33.4		5.2 – 6.1	4.5 – 6.6
(U/L)		1.4 – 18.1	2.0 – 4.1	2.0 – 4.5
Growth hormone (mU/L)	0 – 20	0 - 20	2.0– 14	0.8 – 10.6
Cortisol (µg/mL)	4.3 – 22.4	4.3 – 22.4	4.5 – 20	5 – 19.3

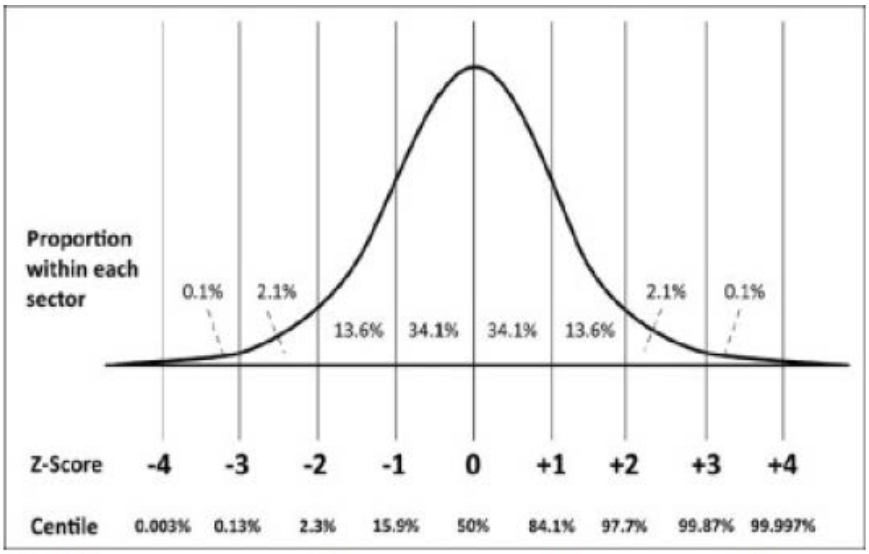
Study NEU_CH_7911

Weight, height and body mass index

Changes in weight, height and BMI should be interpreted with caution due to the imbalance in the age of children at screening (mean age 9.0 years in the Slenyto group and 8.4 years in the placebo group). Overall, there were no clinically significant differences between Slenyto and placebo for weight, height or BMI. BMI Z-scores take account of the age and sex of the child and therefore are preferable for comparing between the treatment groups. Mean changes in BMI Z-score were small in both treatment groups. After 13 weeks of double-blind treatment, BMI Z-score had increased by 0.008 ± 0.3087 in the Slenyto group compared to 0.065 ± 0.4279 in the placebo group. The treatment difference (Slenyto - placebo) was -0.055 [-0.198, 0.088]95% CI, indicating no statistically significant difference between the treatment groups.

The mean BMI Z-score after 91 weeks of open label period was around 1.163 for the Slenyto/Slenyto group and 1.072 for the Placebo/Slenyto group, thus around 1.1 for the total group and with a range of -2.39 to 3.55, which is considered within the normal distribution.

BMI Z-scores after 2 years of treatment on a normal distribution curve



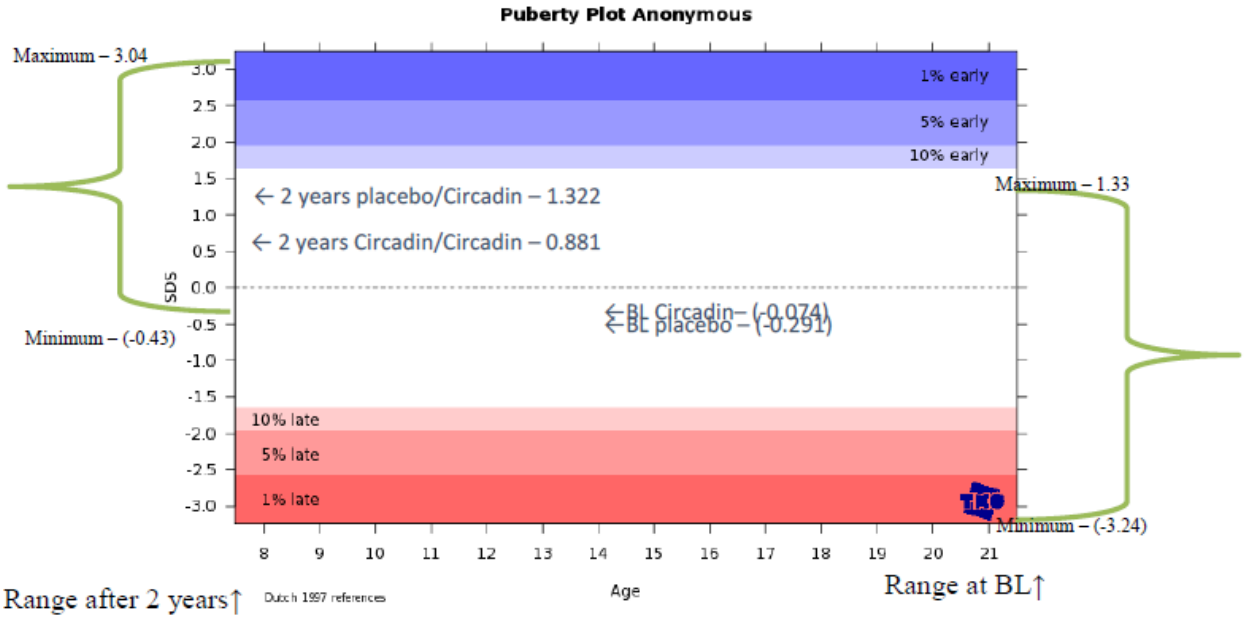
Data source: Tables 14.3.5.7 and Gehring (2017)[33]

Tanner staging

At baseline (Week 2), the Tanner assessments of pubertal development showed a greater proportion of patients in the placebo group were preadolescent compared to the Slenyto group. This difference in pubertal development reflects the slightly lower age of patients in the placebo group at study entry. Change from baseline for SD scores of pubic hair, breast and genitalia development were collected. In the 13-week double-blind phase, there was no apparent difference between Slenyto and placebo. In the 13-week double-blind phase (Week 15) or 13-week open-label phase (Week 28), there was no apparent difference between Slenyto and placebo. At 91-week (Week 106), the mean change from baseline in SD score of pubic hair, breast, and genitalia development increased by almost 1 to 1.5 points in both the treatment groups.

The SD mean scores and minimum and maximum scores after 106 weeks for Slenyto randomized group and the placebo randomized group were put on a line diagram for SD Tanner scale.

Tanner scale pubic hair growth at baseline and after 2 years



Data source: Tables 14.3.6.4, Puberty Plot S-plus package[32]

Epilepsy / seizure frequency

Of the 16 randomized patients with a history of epilepsy, one patient in the placebo group experienced an absence seizure during the double-blind phase of the trial. The seizure was recorded as a non-serious AE, moderate in severity and not related to study treatment. No emergency medication was administered and the patient recovered.

Four patients in Slenyto group and 3 patients in the placebo group were diagnosed with epilepsy.

At Week 54, 2 patients in Slenyto group and 1 patient in placebo group experienced absence seizures (2) and tonic-clonic convulsion (1) during the open-label phase: Patient in Slenyto group experienced seizure that was of 1-minute duration and recorded as non-serious AE, moderate in severity, and unlikely to be related to study treatment. Patient in Slenyto group experienced seizure that was of 1 minute duration. The seizure experienced by patient in the placebo group was recorded as a non-serious AE, mild in severity, unlikely to be related to study treatment and was of 1-minute duration. No emergency medication was administered for the seizures.

There are conflicting data in the literature on the effect of melatonin on epilepsy, with some studies reporting increased seizure frequency, others no change, and yet other studies reporting decreased frequency.

Jain et al. (2015) indicates that melatonin treatment does not worsen seizure frequency in epilepsy. In addition, this appears to be the first study to have measured EEG changes based on spike density, which was non-significantly reduced by melatonin.

Brigo et al. (2016) attempted to perform a meta-analysis of studies on the effects of melatonin on epilepsy, but since the study data was of poor quality, no meta-analysis was performed and thus no conclusions could be drawn.

Safety in special populations

Safety per age subgroup

In the DB period, there were 9 subjects (19.1%) with 24 related AEs in the active group and 11 subjects (20.4%) with 19 related AEs in the placebo group of patients aged 2-12. In the DB period there were 3 subjects (23.1%) with 4 related AEs in the active group and 2 subjects (18.2%) with 3 related AEs in the placebo group of patients aged 13-17. In the OL period there were 14 subjects (18.4%) with 21 related AEs in patients aged 2-12. In the OL period there were 3 subjects (15.8%) with 5 related AEs in patients aged 13-17.

In the DB period, there were 2 subjects (10.5%) with 4 related AEs in the active group and 5 subjects (20%) with 6 related AEs in the placebo group of patients aged 2-6. In the OL period there were 7 subjects (24.1%) with 11 related AEs in patients aged 2-6.

The safety profile of the very young children aged 2-3 years old (that in the pivotal study were diagnosed but in real life might not be diagnosed yet but show autistic traits including sleep disturbances). During the DB period there was one SAE in the placebo group - RESPIRATORY VIRUS - severe not related and no SAEs in the active treatment group. Two treatment related AEs in the placebo group (constipation - possibly related/moderate / intermittent; nightmares - possibly related/mild/ intermittent); no treatment related AEs in the Slenyto group. During the OL period, there were two SAEs unlikely to be related: pneumonia and chest infection mild, and 5 possibly related AEs in four patients, INCREASED EXCITABILITY - possibly related, Mild, INTERMITTENT, Increased hangover feeling, possibly related Mild INTERMITTENT, SINUSITIS - possibly related moderate continued, Fatigue - possibly related; Irritability-mild, fatigue-moderate, - possibly related intermittent.

Use in Pregnancy and Lactation

Melatonin is present in human breast milk and may communicate time of day information to breast-fed infants (Illnerova et al, 1993). Exogenously ingested melatonin may also reach breast milk, and reflect blood concentrations of melatonin with a short delay (Eriksson et al, 1998). Although we have no evidence that melatonin has an effect on breast fed babies, the SmPC text warns against use of the drug in nursing mothers.

Circadin is proposed only for use in patients of 55 years of age or over, and so reproduction toxicity and milk transfer are of little relevance to this age group. Slenyto is indicated in children aged between 2 and 17 years and so pregnant or lactating females may occur in the older age groups. In view of the lack of any clinical data, use of Slenyto in pregnant women and by women intending to become pregnant, or in breast-feeding women is not recommended. No pregnancies have been reported in the studies completed since the marketing authorisation application (Neurim 112006, Neurim 12545A).

Post marketing experience

The safety of the product Circadin is routinely monitored in accordance with the EU Legislation of Pharmacovigilance including PSURs. In accordance, where a potential signal has been observed or new safety data has become available from the completion of clinical studies, the SmPC has been updated where appropriate by the provision of a variation to the existing marketing authorisation.

An estimate of the number of daily doses of Circadin since launch (29 June 2007) has been calculated from sales volumes. These data represent an estimation of patient exposure to Circadin based on the number of packs sold

by Neurim. It is estimated that 6,299,152 patients have been prescribed marketed Circadin up to June 2016. Taking into consideration that children usually take Circadin for longer periods of time than adults, it was estimated that more than a third (~38%) of the patients treated with Circadin between July 2009 and June 2011 in the UK, France and Germany were patients aged <18 years. Children that were prescribed Circadin were diagnosed mainly with psychiatric, mental and developmental disorders.

A total of 1,724 AE reports were received since Circadin was launched in 29 Jun 2007 until to 31 Oct 2016. Out of the 1,724 AE reports, 972 reports were for unauthorised or 'Off-Label' use (56.4%). Of these 972 reports, 517 (53.2%) were either reports of off-label use only or only contained non-adverse drug reaction (ADR) terms such as lack of efficacy. These reports were classified as off-label usage largely because they were given to patients under the age of 55 years (754 reports out of the 972 unauthorised or 'Off-Label' use reports [77.6%]). The most frequent ADRs associated with Circadin were insomnia (97), headache (91), nightmare (84), nausea (78), somnolence (75), dizziness (72), fatigue (57) and restlessness (35).

No safety-related regulatory actions have been taken since product launch.

Data from Food Supplements in the United States

Melatonin has been marketed at doses ranging from 0.5-80 mg as an oral food supplement in the United States for many years and as such falls under the FDA's DSHEA category of "other dietary substance". The in depth evaluation of the literature data on the safety of melatonin became available in April, 2004 when the Committee on the Framework for Evaluating the Safety of Dietary Supplements of the National Academies announced the publication of a report entitled "Dietary Supplements: A Framework for Evaluating Safety". The report contains numerous references to melatonin and includes an 84-page prototype melatonin monograph. Conclusions and recommendations about the safety of the ingredient based on the strength of the scientific evidence were that short-term use of melatonin in a daily amount of 10 mg or less does not raise concern of harm for healthy adults who are not taking concurrent medications or other dietary supplements (Prototype Monograph on Melatonin 2004).

2.10.1. Discussion on clinical safety

Exposure

In adult Circadin studies, a total of 3194 adult patients have received Circadin. In the paediatric Slenyto studies, only 118 children in total have received Slenyto.

However, from the last PSUR in 2013, based on the market experience reported in previous PSURs and the current PSUR, approximately 4,215,047 patients have received Circadin world-wide from its launch to the data-lock date of this PSUR.

No new ADRs have been identified from post-marketing.

Publications from prescription databases in the Scandinavian countries indicate that the majority of melatonin prescriptions are intended for children, the majority of which with concomitant ADHD medication.

Adverse events

The tables on TEAEs and the treatment-related AEs from the paediatric efficacy and safety study don't reveal any new AEs compared to what is already reported for Circadin. In children, somnolence and headache are the only AEs that seem to occur at a markedly higher rate (at least twice as common) in Slenyto treated children compared to placebo. Fatigue, agitation, cough, and dyspnoea were also more frequently reported in the

melatonin group than the placebo group, whereas mood swings and nightmares were less commonly reported in melatonin-treated compared to placebo-treated children.

The proposed SmPC section 4.8 Tabulated list of adverse reactions includes only those AEs that were treatment related from possibly to definitely, that were in more than one child and on a level higher than placebo. The calculations were done based on the sample size of 120 patients from the pivotal study.

During the 39 weeks' open-label extension period with treatment with melatonin at the 2, 5 or 10 mg dose, 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), rhinorrhoea aggression and agitation (5.3% each). However, mood swings occurred more in the placebo than Slenyto group during the double blind period. Since the extension part was an open-label study the mood swings considered treatment related may in fact be due to the underlying disease. The same may be true for aggression and agitation.

There were no deaths in either of the paediatric studies.

In the paediatric efficacy and safety study, 1 patient in the placebo group was hospitalised for SAEs of pneumonia (mild) and respiratory tract infection viral (severe). There were no SAEs in the Slenyto group during the double-blind phase. In the open-label phase, 6 patients experienced SAEs: severe, non-related aggression, moderate non-related constipation, moderate, non-related otitis media, mild lower respiratory tract infection, unlikely related, severe oppositional defiant disorder, unlikely related, moderate non-related eye infection.

There were nine discontinuations due to adverse events, one in the placebo group and two in the treatment group, one during the double-blind phase (fatigue, agitation, and stereotypy) and 8 during the open-label phase (headache, apathy and fatigue, malaise, altered mood, insomnia, trichotillomania, head injury, sinusitis.

Potential side effects

Hormonal effects

The applicant has presented literature data from studies on adult females and males, showing no significant effects of administration of exogenous melatonin on the hypothalamic-pituitary-adrenal (HPA)/ hypothalamic-pituitary-gonadal (HPG) hormones.

However, the fact that melatonin plasma levels are high in prepubertal children and is dramatically reduced during puberty, has led to the suggestion that administration of exogenous melatonin leading to supraphysiological levels in pre-pubertal and pubertal children may lead to pubertal abnormalities. This theoretical concern has somewhat been supported by the fact that melatonin is involved in the hormonal control of seasonally breading animals. There is a lack of long-term safety studies in children investigating the long-term effects of exogenous melatonin on pubertal development.

The duration (13 weeks) of the double-blind phase in the present study was much too short to enable any detection of differences in pubertal development (Tanner staging). The results on BMI Z-score and Tanner scale comparing the data from baseline with those after 2 years of treatment don't suggest any treatment-related effects, but are very blunt since they can only be compared to the normal distribution curve.

In addition to the results from the present study, Geijlswijk et al. in 2011 conducted a long-term safety study of melatonin use in children with ADHD (N=51 children, mean age 12.0 years, 8.6-15.7 years) who took melatonin during a mean time of 3.1 years (min 1.0-max 4.6) at a mean dose of 2.69 mg (0.3-10 mg). The parents

reported Tanner stages of their children (N=46) using a questionnaire. Tanner Stages standard deviation scores did not differ in a statistically significant way from published scores of the general Dutch population of the same age and sex. Since this study did not use physician-collected Tanner staging data but parent-reported Tanner staging, this is of rather low value. However, prescription rates for melatonin use in children and adolescents has been steadily increasing the last decade in many EU countries, and although no safety data has prospectively been collected for these children, the vast use and lack of post-authorisation spontaneous reports on pubertal delays indicates that melatonin cannot possibly have any great impact on puberty development. However, there is a lack of long-term safety data in children. The Applicant agrees to sponsor a non-interventional post authorization safety study (PASS) in case evidence in pubertal development from postmarketing or NEUCH7911 / RTU studies emerges.

Increase in seizures

There have been reports on an increased, decreased or no effect on seizure frequency in patients with epilepsy treated with melatonin. The paediatric Slenyto efficacy study (NEU-CH-7911) was not powered to detect any difference in seizure frequency. Of the 16 randomized patients with a history of epilepsy, one patient in the placebo group experienced an absence seizure during the double-blind phase of the trial and none in the Slenyto group. During the open label phase, 2 patients in Slenyto group and 1 patient in placebo group experienced absence seizures and tonic-clonic convulsion. Since the potential effects on seizures are not known from available data, this should be followed in the PSURs of Slenyto.

2.10.2. Conclusions on clinical safety

The long-term safety up to 2 years of melatonin in children at the 2-5 (-10) mg daily dose is in line with the known safety profile of Circadin in adults and children (post-marketing experience). The concomitant disorders in children with neurodevelopmental disorders differ from the ones in adults aged 55 years and above. There is a need for more long-term safety data on the safety of melatonin in general and more specifically related to pubertal development. However, this could be achieved post-marketing through routine PSURs and a dedicated PASS.

The CHMP considers that the submitted data package supports the use of Slenyto in paediatric population.

2.11. Risk Management Plan

Safety concerns

Summary Table of Safety Concerns

Important identified risks	None
Important potential risks	Delay of sexual maturation and development
Missing information	Use in pregnancy/lactation Long-term safety in children (> 2 years)

Pharmacovigilance plan

The applicant has discussed the feasibility of a study/registry to monitor and assess changes in pubertal development (e.g. onset of puberty or final height). The Applicant also agreed to sponsor a non-interventional post authorization safety study (PASS) in case evidence in pubertal development from post-marketing or NEUCH7911 / RTU studies emerges.

In addition, the applicant agreed to provide, by April 2019, data from the long-term follow up (RTU) and NEUCH7911 studies, in order to evaluate long-term safety.

Summary Table of Risk Minimisation and Pharmacovigilance Activities per Safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important potential risks		
Delay of sexual maturation and development	Routine risk minimization measures: Wording in SmPC Section 4.2, PL section 3 Additional risk minimization measures: None.	Monitor any relevant post marketing safety reports. Reports describing sexual maturation and development would be specifically followed up. RTU – final reporting on 3 years use in the target population by April 2019, and if necessary another registry after April 2019.
Important Missing Information		
Use during pregnancy and lactation	Routine risk minimization measures: Wording in SmPC Section 4.6, PL 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)	Routine risk minimization measures: Wording in SmPC Section 4.2 Additional risk minimization measures: None.	Monitor any relevant post marketing safety reports. Reports related to long term use would be specifically followed up. Final report of the RTU on 3 years use will be submitted on April 2019

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.12. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.13. Product information

2.13.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In children with neurodevelopmental or psychiatric comorbidities, the prevalence of insomnia is as high as 50–75%. This group of children is composed of many subpopulations with varying degrees of impairment and symptomatology, including pervasive developmental disorders (including ASD, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, etc); ADHD; genetic disorders, such as Angelman syndrome; and chronic neurologic disorders, such as epilepsy and Tourette's disorder. 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, characterised by difficulties initiating or staying asleep, and usually far more difficult to treat than their normally developing peers. Some literature data indicate that children with some neurodevelopmental disorders might suffer from low endogenous melatonin secretion and abnormal circadian rhythmicity.

3.1.2. Available therapies and unmet medical need

Currently there are no approved medicinal products indicated for hypnotic use in the paediatric population.

Even though immediate release (IR) melatonin is only an approved medicine in very few European countries (e.g. Hungary) and controlled release melatonin has not been approved for children, it is commonly used off-label in children with neurodevelopmental disorders through individual or general special permission procedures.

3.1.3. Main clinical studies

The pivotal efficacy and safety study was a 13-week placebo-controlled double-blind randomised study in children with ASD and neurogenetic disease using 1 mg tablets of Slenyto at the 2 mg and 5 mg doses. The included study population was children aged 2-17.5 years with ASD or neurogenetic disease (in total 4 patients with Smith-Magenis Syndrome) who suffered from sleep induction and/or sleep maintenance problems and whose sleep problems had not been sufficiently ameliorated by sleep hygiene measures. All patients received the same dose (2 mg Circadin or placebo) during the first 3 weeks of study treatment. Thereafter, the dose could be increased to 5 mg, based on pre-defined criteria. The 13-week placebo-controlled double-blind study was followed by a 91-week open-label study where all subjects received Slenyto at the 2, 5, or 10 mg dose.

The application also included reference to four publications on exploratory, investigator initiated single-centre studies, providing the initial experience in the use of the Reference product (Circadin 2 mg) in three children with myoclonus epilepsy and sleep difficulties (Jan et al, 1999), on 42 multi-disabled children with chronic

sleep-wake cycle disorders (Jan et al, 2000), on 10 children with Smith-Magenis syndrome (De Leersnyder et al, 2003), and on 88 children with various neurodevelopmental disorders (including 47 patients with Smith-Magenis syndrome, 5 patients with Angelman syndrome and 1 patient with Bourneville syndrome (tuberous sclerosis)) (De Leersnyder et al, 2011).

3.2. Favourable effects

A significant increase in total sleep time (+32 min, p=0.034) and a shortened sleep latency (-25 min, p=0.011) and a trend to benefit for longest sleep period (+42 min, p=0.052) as measured by sleep diary were documented in the pivotal study. There were no differences between melatonin and placebo for the secondary endpoints Number of awakenings per night and Wake time after sleep onset were not affected (p=0.474, p=0.981, respectively). The same was true for assessment scales measuring the sleep (composite sleep disturbance index, 0.92 points difference, p=0.074) and daytime behaviour (CGAS: p=0.948, SDQ total score 1.01 points difference, p=0.077) except for the subdomain “Externalizing behaviours” of SDQ, for which melatonin showed a significant effect (0.83 points difference, p=0.021).

Three different assessment scales were used to capture the effects on the caregivers. The caregivers’ well-being scale showed a significant improvement (2.17 points difference, p=0.01), but no statistically significant differences were documented for caregivers’ daytime sleepiness (1.29 points difference, p=0.089),or caregivers’ quality of sleep at night (0.81 points difference, p=0.166).

The main study among the submitted publications (De Leersnyder et al, 2011) reported a reduced sleep latency of 8 min (p<0.001), a prolonged total sleep time of +46 min (p<0.001), a reduction of average awakenings from 1.95 to 0.48 (p<0.001) and a reduction of daytime napping from 39/49 to 8/49 (p<0.001).

3.3. Uncertainties and limitations about favourable effects

Since only total sleep time, sleep latency and the subdomain “Externalizing behaviours” of SDQ were significantly affected in the children, and well-being in the caregivers, this is not fully in line with the EMA guidelines on insomnia, which states that effects on sleep latency or maintenance of sleep should be supported by improvement in quality of day time functioning. The improved well-being of the parents, also being recognised as a secondary endpoint in the section on paediatric trials of the EMA insomnia guideline, offers some support to the notion that Slenyto has beneficial effects in these children. Since younger children with ASD require supervision by their parents/caregivers, the impact of disturbed sleep including awakenings in children with ASD almost always leads to a disturbed sleep of their parents, secondarily affecting their day-time functioning and well-being.

The inclusion criteria in the child efficacy study allowed subjects between 2 and 17.5 years to be included into the study. It is noted that the age span was indeed 2-17 years. 35.2% of the patients were aged 2-6 years, 45,6% aged 7-12 and the remaining 21./% were aged 13-17 years. The efficacy and safety results in these three subgroups based on age appear similar. When analysing the efficacy and safety data from the youngest age group of 2-3 years old children (n=14), it was similar to the results from the other age groups.

Data in patients with neurogentic diseases are very limited, especially in children with Angelman and Bourneville’s disease (Tuberous sclerosis).

Unfavourable effects

During the placebo-controlled 3 months' pivotal trial on children aged 2-17 years with ASD, somnolence (28.3% vs 10.8%), headache (13.3 vs 6.2%), fatigue (23.3 vs 18.5%), agitation (13.3 vs 10.8%), cough (11.7 vs 7.7%) and dyspnoea (10.0 vs 6.2%) were more commonly reported in the melatonin group than the placebo group.

3.4. Uncertainties and limitations about unfavourable effects

The long-term safety of melatonin in children has not been characterised in well-designed studies. Since endogenous plasma concentrations of melatonin increase until puberty, followed by a rapid decrease during puberty, there is a theoretical concern that exogenous administration of melatonin resulting in supra-physiological plasma levels may result in a delay in pubertal development. It is acknowledged that in diseases such as ASD and some of the certain neurogenetic diseases, the endogenous levels of melatonin may be lower than in normally developing children, but effects on puberty cannot be excluded from the limited long-term safety data available. The duration of the current controlled part of the efficacy and safety study in children was not long enough and the number of patients too limited to capture any potential effects on puberty. The applicant has indicated that a report will be available in April 2019 from an RTU in France including 435 children with ASD and neurogenetic diseases. Depending on the results of that report, it will be decided if additional PASS is needed.

3.5. Effects Table

Table 14 Effects Table for Slenyto (data cut-off: 13 Dec 2016).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Total sleep time	Per night	min	+51.16	+18.73	Estimated Difference: +32.43 P=0.034	NEU_CH_7911
Sleep latency	Time until falling asleep in evening	min	-37.88	-12.58	Estimated Difference: -25.30 P=0.011	NEU_CH_7911
Wake time after sleep onset	Wake time during night	min	-13.70	-7.77	Estimated Difference: 0.08 P=0.981	NEU_CH_7911
Number of awakenings per night		number	-0.30	-0.23	Estimated Difference: -0.09 P=0.474	NEU_CH_7911
Longest sleep period	During night	min	+77.93	+25.45	Estimated Difference: 42.16 P=0.052	NEU_CH_7911
Total time in bed per night	Time spent in bed w/wo sleeping	min	+16.03	+1.98	Estimated Difference: 4.75 P=0.713	NEU_CH_7911

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Composite Sleep Disturbance Index (CSDI)		0-12 points in total	-2.4	-1.7	Estimated Difference: -0.92 P=0.074	NEU_CH_7911
Children's Global Assessment Scale (CGAS) score	Social functioning at home, in school, and in community settings	Scale 0-100 points in total	+2.1	+1.4	Estimated Difference: 0.13 P=0.948	NEU_CH_7911
Strength and Difficulties Questionnaire (SDQ) total score	Behavior at home and in school	25 items, 0-2 points each, 0-50 in total	-0.8	+0.2	Estimated Difference: -1.01 P=0.077	NEU_CH_7911
Caregivers' daytime sleepiness (ESS)	Excessive sleepiness scale	8 items, 0-3 points each, 0-24 in total	-0.7	+0.3	Estimated Difference: -1.29 P=0.089	NEU_CH_7911
Caregivers' well-being (WHO-5)		5 items, 0-5 points each, 0-25 in total	+1.3	-0.5	Estimated Difference: 2.17 P=0.01	NEU_CH_7911
Caregivers' quality of sleep at night (PSQI)	Pittsburgh sleep quality index	7 components, each 0-3 points, 0-21 in total	-1.0	-0.5	Estimated Difference: -0.81 P=0.166	NEU_CH_7911
Unfavourable Effects						
Fatigue		%	23.3% 3.3%	18.5% 4.6%	TEAEs ADRs	NEU_CH_7911
Somnolence		%	28.3% 11.7%	10.8% 3.1%	TEAEs ADRs	NEU_CH_7911
Headache		%	13.3% 1.7%	6.2% 0%	TEAEs ADRs	NEU_CH_7911
Seizure frequency		number	0	1	Conflicting literature data	NEU_CH_7911
Pubertal development		Tanner staging	No apparent difference between groups		No long-term data available	NEU_CH_7911

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The magnitude of the favourable effects of Slenyto 2- 10 mg on sleep latency and total sleep time in the pivotal study in patients with ASD, are considered to be of clinical relevance even though it is noted that not all secondary endpoints, including number of awakenings and various other assessments scales on daytime function of the children and caregivers' sleep, were positively affected. The improved sleep endpoints in the children and well-being of the parents are however considered important to the well-being of the child with ASD and the caregivers. In addition, some literature data indicate that children with neurodevelopmental disorders might suffer from low endogenous melatonin secretion and abnormal circadian rhythmicity which may support the documented effect in the pivotal study. This biological rationale is also documented for children with Smith-Magenis Syndrome while the data are more uncertain for the other neurogenetic disorders proposed to be included in the therapeutic indication (Angelman or Bourneville's disease (Tuberous sclerosis)). For Smith-Magenis syndrome, an inverted melatonin diurnal secretion curve has been demonstrated and there is both data from the present study and publications on similar efficacy levels in these children as in children with ASD.

The age cut off of 2 years has been justified by demonstration of similar efficacy and safety in the youngest age group (2-3 years old) compared to the other age groups included in the study. However, not all children with these diseases have received a proper diagnosis at this early age, which may restrict the use of melatonin until they have been diagnosed.

The safety profile in children with ASD appears benign from the present study results with only mild to moderate somnolence, fatigue and headache being the most common ADRs. Somnolence and headache has consistently been reported as AEs of melatonin in the literature, and fatigue, hangover and sudden onset of sleep can be considered belonging to the same spectrum as somnolence, i.e. related to the sedative effects of melatonin.

From the current study, safety data for up to 3 months double-blind treatment and an additional 21 months (91 weeks) open label extension study is available. Thus, it is appropriate to include "Data is available for up to 2 year's treatment" in the SmPC section 4.2. Long term safety data of good quality is still considered too limited to draw any conclusions on long-term safety in general and more specifically the long-term adverse effects on sexual maturation.

"Longer-term safety (>2 years) in children" and "Delay of sexual maturation and development" are included in the list of safety concerns in the RMP. The Applicant also agrees to sponsor a non-interventional post authorization safety study (PASS) in case evidence in pubertal development from postmarketing or NEUCH7911 / RTU studies emerges.

3.7. Balance of benefits and risks

The target population is proposed to be children with ASD and the neurogenetic disease Smith-Magenis Syndrome from the age of 2 years, which can be supported by the results from the pivotal study and literature data.

3.7.1. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Slenyto is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Slenyto is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0148/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.