ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Slenyto 1 mg prolonged-release tablets
Slenyto 5 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Slenyto 1 mg prolonged-release tablets

Each prolonged-release tablet contains 1 mg melatonin.

Excipient with known effect

Each prolonged-release tablet contains lactose monohydrate equivalent to 8.32 mg lactose.

Slenyto 5 mg prolonged-release tablets

Each prolonged-release tablet contains 5 mg melatonin.

Excipient with known effect

Each prolonged-release tablet contains lactose monohydrate equivalent to 8.86 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged- release tablet.

Slenyto 1 mg prolonged-release tablets

Pink, film coated, round, biconvex, 3 mm diameter tablets with no imprint.

Slenyto 5 mg prolonged-release tablets

Yellow, film coated, round, biconvex, 3 mm diameter tablets with no imprint.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Insomnia in children and adolescents aged 2-18 years with Autism Spectrum Disorder (ASD) and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings
The recommended starting dose is 2 mg of Slenyto. If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg.

Slenyto should be taken once daily, 0.5-1 hour before bedtime and with or after food.

Data are available for up to 2 years' treatment. The patient should be monitored at regular intervals (at least every 6 months) to check that Slenyto is still the most appropriate treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment.

If a tablet is forgotten, it could be taken before the patient goes to sleep that night, but after this time, no other tablet should be given before the next scheduled dose.

Insomnia in children and adolescents aged 6-17 years with ADHD
The recommended starting dose is 1-2 mg. The dose may be adjusted on an individual basis to 5 mg per day regardless of age of the child. If clinically needed, the maximum daily dose may be increased to 10 mg. The lowest effective dose should be taken for the shortest period.
Slenyto should be taken once daily, 0.5-1 hour before bedtime and with or after food.

After approximately 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be monitored regularly (at least every 6 months) to check that Slenyto is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, at least once a year.

If a tablet is forgotten, it could be taken before the patient goes to sleep that night, but after this time, no other tablet should be given before the next scheduled dose.

Special populations

Renal impairment
The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to patients with renal impairment.

Hepatic impairment
There is no experience of the use of melatonin in patients with liver impairment. Therefore, melatonin is not recommended for use in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Slenyto have not been established for children under 6 years of age with ADHD.

There is no relevant use of melatonin in children aged 0 to 2 years for the treatment of insomnia.

Method of administration

Oral use. Tablets should be swallowed whole. The tablet should not be broken, crushed or chewed because it will lose the prolonged release properties.

Tablets can be put into food such as yoghurt, orange juice or ice-cream to facilitate swallowing and improve compliance. If the tablets are mixed with food or drink, they should be taken immediately and the mixture not stored.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Drowsiness

Melatonin may cause drowsiness and residual effects such as daytime fatigue may occur. These effects should be considered, particularly in children and adolescents with ADHD, as they may exacerbate daytime symptoms like inattention, hyperactivity, or behavioural disturbances. Caregivers and healthcare professionals should monitor patients for signs of daytime fatigue and adjust the dosing schedule or discontinue treatment if such effects impair daily functioning. Therefore, the medicinal product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety (see section 4.7).

Autoimmune diseases

No clinical data exist concerning the use of melatonin in individuals with autoimmune diseases. Therefore, melatonin is not recommended for use in patients with autoimmune diseases.

Interactions with other medicines and alcohol

Concomitant use with fluvoxamine, alcohol, benzodiazepines/non-benzodiazepines hypnotics, thioridazine and imipramine is not recommended (see section 4.5).

Lactose

Slenyto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults. In the absence of specific studies in children, the drug interactions with melatonin are those known in adults.

Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible.

Concomitant use not recommended

Concomitant use of the following medicinal products and alcohol is not recommended (see section 4.4):

Fluvoxamine
Fluvoxamine increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum C_{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.

Alcohol
Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.

Benzodiazepines/non-benzodiazepine hypnotics
Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone. Combination with benzodiazepines and non-benzodiazepine hypnotics should be avoided.

Thioridazine and imipramine
Melatonin has been co-administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, melatonin co-administration resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone, and increased feelings of "muzzy-headedness" compared to thioridazine alone. Combination with thioridazine and imipramine should be avoided.

Concomitant use to be considered with caution

Concomitant use of the following medicinal products should be considered with caution:

5- or 8-methoxypsoralen
Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 or 8-MOP), which increases melatonin levels by inhibiting its metabolism.

Cimetidine
Caution should be exercised in patients on cimetidine which is a potent inhibitor of certain cytochrome P450 (CYP450) enzymes, mainly CYP1A2 and thereby increases plasma melatonin levels, by inhibiting its metabolism.

Oestrogens
Caution should be exercised in patients on oestrogens (e.g. contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.

CYP1A2 inhibitors
CYP1A2 inhibitors such as quinolones (ciprofloxacin and norfloxacin) may give rise to increased melatonin exposure.

CYP1A2 inducers
CYP1A2 inducers such as carbamazepine and rifampicin may reduce plasma concentrations of melatonin. Therefore, when CYP1A2 inducers and melatonin are both given, dose adjustment may be required.

Smoking

Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with melatonin, dose adjustment may be required.

NSAIDs

Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen, given in the evening may suppress endogenous melatonin levels in the early part of the night by up to 75%. If possible, administration of NSAIDs should be avoided in the evening.

Beta-blockers

Beta-blockers may supress the night-time release of endogenous melatonin and thus should be administered in the morning.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of melatonin in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of melatonin during pregnancy.

Breastfeeding

Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. Data in animals indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. The effect of melatonin on newborns/infants is unknown.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from melatonin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

In studies performed in both adult and juvenile animals, melatonin had no effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Melatonin has a moderate influence on the ability to drive and use machines.

Melatonin may cause drowsiness, therefore melatonin should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions with Slenyto in clinical studies were somnolence, fatigue, mood swings, headache, irritability, aggression and hangover occurring in 1:100-1:10 children.

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common
Psychiatric disorders	Mood swings, Aggression, Irritability
Nervous system disorders	Somnolence, Headache, Sudden onset of sleep
Respiratory, thoracic and mediastinal disorders	Sinusitis
General disorders and administration site conditions	Fatigue, Hangover

The following adverse reactions (frequency unknown) have been reported with off-label use of the adult formulation, 2 mg prolonged-release melatonin tablets: epilepsy, visual impairment, dyspnoea, epistaxis, constipation, decreased appetite, swelling face, skin lesion, feeling abnormal, abnormal behaviour and neutropenia.

Furthermore, in ASD and neurogenetic children treated with 2-6 mg of the adult formulation under a Temporary Recommendation for Use (RTU) program in France (N=926), the following additional adverse reactions (frequency uncommon) have been reported: depression, nightmares, agitation and abdominal pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

If overdose occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists, ATC code: N05CH01

Mechanism of action

The activity of melatonin at the melatonin receptors (MT1, MT2 and MT3) is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

Clinical efficacy and safety in the paediatric population

ASDs and Smith-Magenis syndrome
Efficacy and safety have been assessed in a randomised, placebo-controlled study in children diagnosed with ASDs and neurodevelopmental disabilities caused by Smith-Magenis syndrome who had not shown improvement after standard sleep behavioural intervention. Treatment was administered for up to two years.

The study comprises 5 periods: 1) pre-study period (4 weeks), 2) baseline single-blind placebo period (2 weeks), 3) randomized placebo-controlled treatment period (13 weeks), 4) open label treatment period (91 weeks), and 5) single blind run-out period (2 weeks placebo).

A total of 125 children (2-17.0 years of age, mean age 8.7 +/- 4.15; 96.8% ASD, 3.2% Smith-Magenis syndrome [SMS]) whose sleep failed to improve on behavioural intervention alone were randomized

and 112 weeks' results are available. 28.8% patients were diagnosed with ADHD before study initiation and 77% had abnormal SDQ hyperactivity/inattention score (>=7) at baseline.

Randomized placebo-controlled treatment period results (13 weeks)
The study met the primary endpoint, demonstrating statistically significant effects of Slenyto 2/5 mg versus placebo on change from baseline in mean Sleep and Nap Diary (SND)-assessed Total Sleep Time (TST) after 13 weeks of double-blind treatment. At baseline, mean TST was 457.2 minutes in the Slenyto and 459.9 minutes in the placebo group. After 13 weeks of double-blind treatment, participants slept on average 57.5 minutes longer at night with Slenyto compared to 9.1 minutes with placebo adjusted mean treatment difference Slenyto–placebo 33.1 minutes in the all Randomized Set; Multiple Imputation (MI) (p=0 .026).

At baseline, mean Sleep Latency (SL) was 95.2 minutes in the Slenyto and 98.8 minutes in the placebo group. By the end of the 13-week treatment period, children fell asleep on average 39.6 minutes faster with Slenyto and 12.5 minutes faster with placebo adjusted mean treatment difference -25.3 minutes in the all Randomized Set; MI(p=0.012) without causing earlier wakeup time. The rate of participants attaining clinically meaningful responses in TST (increase of 45 minutes from baseline) and/or SL (decrease of 15 minutes from baseline) was significantly higher with Slenyto than with placebo (68.9% versus 39.3% respectively; p=0 .001).

Besides shortening of SL, increase in the longest sleep episode (LSE) = uninterrupted sleep duration compared to placebo was observed. By the end of the 13-week double-blind period, the mean LSE increased on average by 77.9 minutes in the Slenyto treated group, compared to 25.5 minutes in the placebo-treated group. The adjusted estimated treatment differences were 43.2 minutes in the all Randomized Set (MI, p=0 .039). Wake up time was unaffected; after 13 weeks, patients' wake up time was delayed insignificantly by 0.09 hour (0.215) (5.4 minutes) with Slenyto compared to placebo treatment.

Slenyto 2 mg/5 mg treatment resulted in a significant improvement over placebo in the child's externalizing behaviours (hyperactivity/inattention+ conduct scores) as assessed by the Strength and Difficulties Questionnaire (SDQ) after 13 weeks of double-blind treatment (p=0.021). For the total SDQ score after 13 weeks of double blind treatment, there was a trend to benefit in favour of Slenyto (p=0.077). For social functioning (CGAS), the differences between Slenyto and placebo were small and not statistically significant (Table 1).

Table 1: CHILD BEHAVIOUR (13 weeks Double-blind)

Variable	Group	Adjusted treatment means (SE) [95% CI]	Treatment difference (SE)	95% CI	p-value*
		SDQ			
Externalizing behaviours	Slenyto Placebo	-0.70 (0.244)[-1.19;-0.22] 0.13(0.258)[-0.38; 0.64]	-0.83 (0.355)	-1.54,-0.13	0.021
Total score	Slenyto Placebo	-0.84 (0.387) [-1.61, -0.07] 0.17 (0.409) [-0.64, 0.98]	-1.01 (0.563)	-2.12, 0.11	0.077
		CGAS			
	Slenyto Placebo	1.96(1.328)(-0.67,4.60) 1.84(1.355)(-0.84,4.52)	0.13(1.901)	-3.64,3.89	ns

*MMRM analysis CI = confidence interval; SDQ = Strength and Difficulties Questionnaire; CGAS = the Children's Global Assessment Scale; SE = standard error

The treatment effects on sleep variables were associated with improved parents' well-being. There was a significant improvement with Slenyto over placebo in Composite Sleep Disturbance Index (CSDI) - assessed parent satisfaction in child sleep pattern (p=0 .005) and in caregivers' well-being as assessed by the WHO-5 after 13 weeks of double-blind treatment (p=0.01) (Table 2).

Table 2: PARENTS WELL BEING (13 weeks Double- blind)					
Variable	**Group**	**Adjusted treatment means (SE) [95% CI]**	**Treatment difference (SE)**	**95% CI**	**p-value***
WHO-5	Slenyto Placebo	1.43(0.565)(0.31,2.55) -0.75(0.608)(-1.95,0.46)	2.17(0.831)	0.53,3.82	0.01
CSDI satisfaction	Slenyto Placebo	1.43(0.175)(1.08,1.78) 0.71(0.184)(0.34,1.07)	0.72(0.254)	0.22,1.23	0.005

*MMRM analysis CI = confidence interval; WHO-5= the World Health Organization Well-Being Index; CSDI = Composite Sleep Disturbance Index; SE = standard error

Open label treatment period results (91weeks)
Patients (51 from the Slenyto group and 44 from the placebo group, mean age 9 ± 4.24 years, range 2-17.0 years) received open-label Slenyto 2/5 mg according to the double-blind phase dose, for 91 weeks with optional dose adjustment to 2, 5 or 10 mg/day after the first 13 weeks of follow-up period. 74 patients completed 104 weeks of treatment, 39 completed 2 years and 35 completed 21 months of 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 throughout the 39 weeks' follow up period.

After 2 weeks withdrawal on placebo, a descriptive reduction in most scores was seen but levels were still significantly better than baseline levels with no signs of rebound effects.

ADHD
In the Slenyto study described above, 36 participants in addition to ASD had an ADHD diagnosed in their medical history. Analysis of the effects of Slenyto on the primary endpoint, TST, demonstrated the same level of improvement in participants with and without ADHD comorbidity.

Melatonin treatment has been studied in a 4-week randomized, double-blind, placebo- controlled study conducted in 105 children between 6 - 12 years of age, with ADHD and chronic sleep onset insomnia who did not receive ADHD medications or behavioural intervention (van der Heijden KB et al. 2007). In this study, immediate release melatonin supplementation was used at a dose of 3 mg or 6 mg for 4 weeks. Melatonin treatment advanced circadian rhythms of sleep-wake and shortened sleep latency in children with ADHD and chronic sleep onset insomnia. Mean sleep latency decreased by 21.3 minutes in the melatonin group and increased by 3 minutes in the placebo group. Total time asleep increased by 19.8 minutes in the melatonin group and decreased by 13.6 minutes in the placebo group. Immediate release melatonin had no effect on problem behaviour, cognitive performance, or quality of life.

5.2 Pharmacokinetic properties

Absorption

In the paediatric population comprising 16 ASD children ages 7-15 years old suffering from insomnia, following Slenyto 2 mg (2 x 1 mg mini-tablets) administration after a standardized breakfast, melatonin concentrations peaked within 2 hours after administration and remained elevated for 6 hours thereafter with a C_{max} (SD) of 410 pg/ml (210) in the saliva.

In adults, following Slenyto 5 mg (1 x 5 mg mini-tablet) administered after food, melatonin concentrations peaked within 3 hours after administration; C_{max} (SD) was 3.57 ng/ml (3.64) in plasma. Under fasted conditions C_{max} was lower (1.73 ng/ml) and t_{max} was earlier (within 2 hours) with a minor effect on AUC-∞ that was slightly reduced (-14%) as compared to fed state.

The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50% in the elderly. The kinetics of melatonin are linear over the range of 2-8 mg.

Data with 2 mg prolonged release melatonin tablets and data with 1 mg and 5 mg mini-tablets indicate that there is no accumulation of melatonin after repeated dosing. This finding is compatible with the short half-life of melatonin in humans.

Bioavailability is in the order of 15%. There is a significant first pass effect with an estimated first pass metabolism of 85%.

Distribution

The *in vitro* plasma protein binding of melatonin is approximately 60%. Melatonin is mainly bound to albumin, alpha$_1$-acid glycoprotein and high density lipoprotein.

Biotransformation

Melatonin undergoes a fast first hepatic pass metabolism and is metabolised predominantly by CYP1A enzymes, and possibly CYP2C19 of the cytochrome P450 system with elimination half life of ca 40 minutes. Prepubertal children and young adults metabolize melatonin faster than adults. Altogether, melatonin metabolism declines with age, with pre-pubertal and pubertal metabolism faster than at older age. The principal metabolite is 6-sulfatoxy-melatonin (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Melatonin does not induce CYP1A2 or CYP3A enzymes in vitro at supra-therapeutic concentrations.

Elimination

Terminal half life ($t_{½}$) is 3.5-4 hours. Two liver-mediated metabolic pathways account for around 90% of melatonin metabolism. The predominant metabolic flux is through hydroxylation at C6 via the hepatic microsome P-450 system to yield 6-hydroxymelatonin. The second, less significant, pathway is 5-demethylation to yield a physiological melatonin precursor, N-acetylserotonin. Both 6-hydroxymelatonin and N-acetylserotonin are ultimately conjugated to sulfate and glucoronic acid, and excreted in the urine as their corresponding 6-sulfatoxy and 6-glucoronide derivatives.

Elimination is by renal excretion of metabolites, 89% as sulfated and glucoronide conjugates of 6-hydroxymelatonin (over 80% as 6-sulfatoxy melatonin) and 2% is excreted as melatonin (unchanged active substance).

Gender

A 3-4-fold increase in C_{max} is apparent for women compared to men. A five-fold variability in C_{max} between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations

Renal impairment
There is no experience of the use of melatonin in paediatric patients with renal impairment (see Section 4.2). However as melatonin is mainly eliminated via liver metabolism, and the metabolite 6-SMT is inactive, renal impairment is not expected to influence clearance of melatonin.

Hepatic impairment
The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.

Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

There is no experience of the use of melatonin in paediatric patients with liver impairment. Published data demonstrate markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment (see Section 4.2).

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

A slight effect on post-natal growth and viability was found in rats only at very high doses, equivalent to approximately 2000 mg/day in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Slenyto 1 mg prolonged-release tablet

Tablet core
Ammonio methacrylate copolymer type B
Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Silica, colloidal anhydrous
Talc
Magnesium stearate

Film coating
Carmellose sodium (E466)
Maltodextrin
Glucose monohydrate
Lecithin (E322)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)

Slenyto 5 mg prolonged-release tablet

Tablet core
Ammonio methacrylate copolymer type A
Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

Film coating
Carmellose sodium (E466)
Maltodextrin
Glucose monohydrate
Lecithin (E322)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Slenyto 1 mg prolonged-release tablets

PVC/PVDC opaque blister with aluminium foil backing. Pack size: 30 tablets or 60 tablets.

Slenyto 5 mg prolonged-release tablets

PVC/PVDC opaque blister with aluminium foil backing. Pack size: 30 tablets or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL
4 rue de Marivaux
75002 Paris
France
e-mail: regulatory@neurim.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1318/001
EU/1/18/1318/003
EU/1/18/1318/005
EU/1/18/1318/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018
Date of latest renewal: 5 June 2023

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Iberfar Indústria Farmacêutica S.A.,
Estrada Consiglieri Pedroso 123, Queluz De Baixo,
Barcarena,
2734-501,
Portugal

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (BLISTER PACK) – 1 MG

1. NAME OF THE MEDICINAL PRODUCT

Slenyto 1 mg prolonged-release tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 1 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
60 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole. Do not break, crush or chew the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL
4 rue de Marivaux
75002 Paris
France
e-mail: regulatory@neurim.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1318/005: 30 prolonged-release tablets
EU/1/18/1318/001: 60 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Slenyto 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 30 TABLETS – 1 MG

1. NAME OF THE MEDICINAL PRODUCT

Slenyto 1 mg prolonged-release tablets
melatonin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (BLISTER PACK) – 5 MG

1. NAME OF THE MEDICINAL PRODUCT

Slenyto 5 mg prolonged-release tablets
melatonin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 5 mg melatonin.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole. Do not break, crush or chew the tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL
4 rue de Marivaux
75002 Paris
France
e-mail: regulatory@neurim.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1318/003: 30 prolonged-release tablets
EU/1/18/1318/006: 100 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Slenyto 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER STRIP OF 25 OR 30 TABLETS – 5 MG

1. NAME OF THE MEDICINAL PRODUCT

Slenyto 5 mg prolonged-release tablets
melatonin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Slenyto 1 mg prolonged-release tablets
Slenyto 5 mg prolonged-release tablets
melatonin

Read all of this leaflet carefully before you or your child starts taking this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or your child's.
- If you or your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Slenyto is and what it is used for

What Slenyto is
Slenyto is a medicine that contains the active ingredient, melatonin. Melatonin is a hormone produced naturally by the body.

What it is used for

Slenyto is used for treatment of **insomnia** (sleeplessness) in:
- **children and adolescents** (aged 2 to 18 years old) with **autism spectrum disorder (ASD**) and/or **neurogenetic diseases** (inherited conditions affecting the nerves and brain) associated with abnormal levels of melatonin and/or night-time awakenings, where other healthy sleeping routines (such as a regular bedtime and soothing sleeping environment) have not worked well enough.
- **children and adolescents** (aged 6 to 17 years old) with **attention-deficit hyperactivity disorder (ADHD)** where other healthy sleeping routines (such as a regular bedtime and soothing sleeping environment) have not worked well enough.

Slenyto shortens the time it takes to fall asleep and lengthens the duration of sleep. The medicine can help you or your child fall asleep and may help you or your child sleep for longer during the night.

2. What you need to know before you or your child takes Slenyto

DO NOT take Slenyto if you or your child
- is allergic to melatonin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Slenyto if you or your child:

- has liver or kidney problems. You should speak to your doctor before taking/giving Slenyto as its use is not recommended in such cases.
- suffers from an autoimmune disease (where the body's own immune (defence) system attacks parts of the body). You should speak to your doctor before taking/giving Slenyto as its use is not recommended in such cases.

Slenyto may cause drowsiness and daytime fatigue. Caregivers should monitor the child for signs of daytime fatigue and contact their doctor for advice if symptoms occur.
In particular, children and adolescents with ADHD may have increased daytime symptoms like inattention, hyperactivity, or behavioural disturbances.

Children

The safety and efficacy of Slenyto have not been established for children under 6 years of age with ADHD.

Do not give this medicine to children below the age of 2 years as it has not been tested and its effects are unknown.

Other medicines and Slenyto

Tell your doctor or pharmacist if you or your child is taking, has recently taken or might take any other medicines.

In particular, taking Slenyto with the following medicines can increase the risk of side effects, or it can affect the way that Slenyto or the other medicine works:

- **fluvoxamine** (used for the treatment of depression and obsessive compulsive disorder)
- **methoxypsoralens** (used in the treatment of skin disorders e.g. psoriasis)
- **cimetidine** (used in the treatment of stomach problems such as ulcers)
- **quinolones** (for example ciprofloxacin and norfloxacin) and **rifampicin** (used in the treatment of bacterial infections)
- **oestrogens** (used in contraceptives or hormone replacement therapy)
- **carbamazepine** (used in the treatment of epilepsy)
- **non-steroidal anti-inflammatory medicines** such as aspirin and ibuprofen (used for treating pain and inflammation). These medicines should be avoided, especially in the evening.
- **beta-blockers** (used to control blood pressure). These medicines should be taken in the morning.
- **benzodiazepines** and **non-benzodiazepine hypnotics** such as zaleplon, zolpidem and zopiclone (used to induce sleep)
- **thioridazine** (used for the treatment of schizophrenia)
- **imipramine** (used for the treatment of depression)

Smoking
Smoking can increase the breakdown of melatonin by the liver, which may make this medicine less effective. Please tell your doctor if you or your child starts or stops smoking during treatment.

Slenyto with alcohol
Do not drink alcohol before, during or after taking Slenyto, because alcohol weakens the effect of the medicine.

Pregnancy and breast-feeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Tell your doctor or pharmacist before using Slenyto if you or your daughter:
- is pregnant or might be pregnant. As a precautionary measure, it is preferable to avoid the use of melatonin during pregnancy.
- is breast-feeding or planning to breast-feed. It is possible that melatonin is passed into human breast milk, therefore your doctor will decide whether you or your daughter should breastfeed whilst taking melatonin.

Driving and using machines
Slenyto may cause drowsiness. After taking this medicine, you or your child should not drive a vehicle, ride a bicycle, or use machinery until completely recovered.

If you or your child suffers from continued drowsiness, you should consult your doctor.

Slenyto contains lactose
Slenyto contains lactose monohydrate. If you or your child has been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Slenyto

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Slenyto is available in two strengths: 1 mg and 5 mg.

Insomnia in children and adolescents (aged 2 to 18 years old) with ASD and/or neurogenetic diseases (inherited conditions affecting the nerves and brain) associated with abnormal levels of melatonin and/or night-time awakenings.

The recommended starting dose is 2 mg (two 1-mg tablets) once daily. If there is no improvement in your/your child's symptoms, your doctor may increase the dose of Slenyto to find the most suitable dose for you/your child. The maximum daily dose that you/your child will receive is 10 mg (two 5-mg tablets).

You or your child should be monitored by your doctor at regular intervals (recommended every 6 months) to check that Slenyto is still the right treatment for you/them.

Insomnia in children and adolescents (aged 6 to 17 years old) with ADHD

The recommended starting dose is 1-2 mg (one to two 1-mg tablets) once daily. If there is no improvement in your/your child's symptoms, the dose may be adjusted individually to 5 mg daily, regardless of age. If the doctor considers it necessary, the maximum daily dose may be increased to 10 mg (two 5-mg tablets) daily.

The lowest dose possible will be given, for the shortest possible time.
You or your child should be monitored by your doctor at regular intervals (recommended every 6 months) to check that Slenyto is still the right treatment for you/them.
Treatment should be interrupted once a year to see if treatment is still needed.

<u>When to take Slenyto</u>
Slenyto should be taken in the evening, 30 to 60 minutes before bedtime. The tablets should be taken after the evening meal, i.e. on a full stomach.

How to take Slenyto
Slenyto is for oral use. **The tablets should be swallowed whole and NOT broken, crushed or chewed**. Crushing and chewing damages the special properties of the tablet and means that they will not work properly.

The whole tablets can be put into food like yoghurt, orange juice or ice-cream to help with swallowing. If the tablets are mixed with these foods, they should be given immediately and not left or stored, as this may affect the way the tablets work. If the tablets are mixed with any other type of food, the tablets may not work properly.

If you or your child takes more Slenyto than you/they should
If you/your child has accidentally taken too much medicine, contact the doctor or pharmacist as soon as possible.

Taking more than the recommended daily dose may make you/your child feel drowsy.

If you or your child forgets to take Slenyto
If you or your child forgets to take a tablet, it could be taken before going to sleep that night, but after this time, no other tablet should be taken before the next evening.
Do not take a double dose to make up for a forgotten dose.

If you or your child stops taking Slenyto
You should talk to your doctor before you/your child stops taking Slenyto. It is important to continue taking this medicine to treat the condition.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Unexpected changes in behaviour, such as aggression, may occur commonly (affecting between 1 in 100 to 1 in 10 people). **If this change in behaviour occurs, you must tell your doctor. The doctor may want you/your child to stop taking this medicine.**

If any of the following side effects get serious or are troublesome, contact your doctor or seek medical advice:

Common: may affect between 1 in 100 to 1 in 10 people

- Changes in mood
- Aggression
- Irritability
- Drowsiness
- Headache
- Sudden onset of sleep
- Swelling and inflammation of the sinuses associated with pain and blocked nose (sinusitis)
- Tiredness
- Hangover feeling

Uncommon: may affect between 1 in 1000 to 1 in 100 people

- Depression
- Nightmares
- Agitation

- Stomach ache

Frequency not known (reported with another pharmaceutical form and strength)

- Fits (epilepsy)
- Visual impairment
- Breathlessness/shortness of breath (dyspnoea)
- Nose bleeds (epistaxis)
- Constipation
- Decreased appetite
- Swelling of the face
- Skin lesion
- Feeling abnormal
- Abnormal behaviour
- Low levels of white blood cells (neutropenia)

Reporting of side effects
If you or your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Slenyto

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Slenyto contains

1 mg strength

- The active substance is melatonin. Each tablet contains 1 mg melatonin.
- The other ingredients are ammonio methacrylate copolymer type B, calcium hydrogen phosphate dihydrate, lactose monohydrate, silica (colloidal anhydrous), talc, magnesium stearate, carmellose sodium (E466), maltodextrin, glucose monohydrate, lecithin (E322), titanium dioxide (E171), iron oxide red (E172) and iron oxide yellow (E172).

5 mg strength

- The active substance is melatonin. Each tablet contains 5 mg melatonin.
- The other ingredients are ammonio methacrylate copolymer type A, calcium hydrogen phosphate dihydrate, lactose monohydrate, silica (colloidal anhydrous), magnesium stearate, carmellose sodium (E466), maltodextrin, glucose monohydrate, lecithin (E322), titanium dioxide (E171) and iron oxide yellow (E172).

What Slenyto looks like and contents of the pack

1 mg strength

Slenyto 1 mg prolonged-release tablets are pink, film coated, round, biconvex, 3 mm diameter tablets.

Available in blister packs of 30 / 60 tablets.

5 mg strength

Slenyto 5 mg prolonged-release tablets are yellow, film coated, round, biconvex, 3 mm diameter tablets.

Available in blister packs of 30 / 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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This leaflet was last revised in { month/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu