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 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.

4.2 Posology and method of administration

Posology

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.

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 (under 2 years of age)
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. 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

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 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=731), 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
/https://sideeffects.health.gov.il

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

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.

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
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Ammonio methacrylate ,Copolymer, type B (Eudragit RSPO®)
Talcum
Silica, colloidal anhydrous (Aerosil®)
Magnesium stearate

Film coating
Sodium Carboxymrthylcellulose
Maltodextrin
Dextrose monohydrate
Lecithin
Titanium dioxide
Iron oxide, red
Iron oxide, yellow

Slenyto 5 mg prolonged-release tablet

Tablet core
Lactose monohydrate
Ammonio methacrylate, Copolymer, type A (Eudragit RLPO®)
Calcium hydrogen phosphate dihydrate
Silica, colloidal anhydrous (Aerosil®)
Magnesium stearate

Film coating
Sodium Carboxymrthylcellulose
Maltodextrin
Dextrose monohydrate
Lecithin
Titanium dioxide
Iron oxide, yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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: 60 tablets.

Slenyto 5 mg prolonged-release tablets

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

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

Neurim Pharmaceuticals (1991) Limited
HaBarzel st. 27
Tel Aviv

8. Registration Number

Slenyto 1 mg: 165-84-36331-00
Slenyto 5 mg: 165-85-36332-00

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