AUSTRALIAN PRODUCT INFORMATION – SLENYTO® PROLONGED RELEASE TABLETS (MELATONIN)

1 NAME OF THE MEDICINE

Melatonin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SLENYTO 1 mg and 5 mg prolonged release tablets.

The active ingredient in SLENYTO prolonged release tablets is a melatonin NOT of plant or animal origin.

Excipient with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended starting daily dose is 2 mg of SLENYTO. If an inadequate response has been observed, the daily dose should be increased to 5 mg, with a maximal dose of 10 mg. In the clinical study, the treatment with 10 mg of melatonin was required only for a small group of children. The magnitude of increase in Total Sleep Time with 10 mg was not the same as with 2 mg and 5 mg doses of melatonin (see also section 5.1 Pharmacodynamic properties, Clinical trials).

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

Data is available for up to 2 year's 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.

Behavioural interventions should be continued while on treatment with melatonin.

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.

Paediatric population (under 2 years of age)

SLENYTO has not been studied in children under 2 years of age. There is no relevant use of SLENYTO in children aged 0 to 2 years for the treatment of insomnia.

Adult population

SLENYTO is indicated for the paediatric population only.

Renal insufficiency

The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied (see Section 5.2 Pharmacokinetic properties).

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 Pharmacokinetic properties).

4.3 CONTRAINDICATIONS

SLENYTO prolonged release tablets are contraindicated in patients with a known hypersensitivity to any ingredient of the product (see Section 6.1 List of excipients).

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.

Autoimmune diseases

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

Excipients

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in the elderly

SLENYTO is indicated for use for the paediatric population only.

Paediatric use

There is no relevant use of SLENYTO in children aged 0 to 2 years for the treatment of insomnia. Therefore SLENYTO is not recommended for use in children below 2 years of age.

Effects on laboratory tests

No information is available on the effect of melatonin on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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. In clinical trials, psychotropic medications were only included if study participants were on stable dose of non-excluded medication (anti-epileptics, anti-depressants, stimulants, mood changing drugs, anti-psychotics, alpha agonists and beta blockers) for 3 months prior to randomisation.

Concomitant use not recommended

Fluvoxamine - Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and 12-fold higher serum Cmax) 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.

Alcohol affects the dissolution profile of SLENYTO *in-vitro,* therefore the prolonged release characteristics of SLENYTO may be altered by alcohol, resulting in immediate release of melatonin. Medicines containing alcohol e.g. cough medicines should not be taken with SLENYTO.

Benzodiazepines and 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

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

Cimetidine - Coadministration of melatonin with cimetidine resulted in a 1.7 fold increase in exposure to melatonin with no change in the exposure to cimetidine.

Caution should be exercised in patients on cimetidine, a CYP2D inhibitor which increases plasma melatonin levels by inhibiting its metabolism.

Cigarette smoking - Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.

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

Hepatic enzymes - Melatonin has been observed to induce CYP3A in vitro at supra-therapeutic concentrations. The clinical relevance of the finding is unknown. If induction occurs, plasma concentrations of concomitantly administered drugs can be reduced.

Melatonin does not appear to induce CYP1A enzymes *in vitro* at supra-therapeutic concentrations. Therefore, interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant.

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:

Quinolones - CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.

Carbamazepine and rifampicin - CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.

NSAIDs- Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen, given in the evening may suppress the 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

Effects on fertility

No significant effects on fertility or reproductive performance were observed in rats given oral melatonin prior to mating through to early gestation at doses over 900-fold the clinical dose of 2 mg in adults, based on body surface area.

Use in pregnancy – Pregnancy Category B3

No significant effects on embryofetal development were observed in rats given oral melatonin during the period of organogenesis at doses over 900-fold the clinical dose of 2 mg in adults, based on body surface area.

No clinical data on exposed pregnancies are available. In view of the lack of clinical data, use in pregnant women and by women intended to become pregnant is not recommended.

Use in lactation

Maternal transfer of exogenous melatonin to the fetus via the placenta or milk has been demonstrated in several animal species including rats, hamsters, goats, monkeys and cows. A slight reduction in post-natal growth, viability and development was found in rats given oral melatonin during gestation through weaning at doses over 900-fold the clinical dose of 2 mg in adults, based on body surface area; the no-effect dose was over 250-fold the clinical dose.

Endogenous melatonin has been detected in human breast milk, thus exogenous melatonin is likely excreted into human milk. The effects of melatonin on the nursing infant have not been established. Therefore, breast-feeding is not recommended in women under treatment with melatonin.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Melatonin has negligible influence on the ability to drive and use machines. Nevertheless, patients should avoid engaging in hazardous activities (such as driving or operating machinery) after taking melatonin.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events reported in paediatric trials

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.

Table 1: Adverse events in paediatric trials

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In general, the main therapy for all overdoses is supportive and symptomatic care.

Symptoms

If overdose occurs, drowsiness is to be expected. No case of overdose has been reported. melatonin has been administered at 5 mg daily doses in clinical trials over 12 months without significantly changing the nature of the adverse reactions reported.

Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature.

Treatment

Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or National Poisons Centre on 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Melatonin Receptor Agonists, ATC code: N05CH01

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

Mechanism of action

The activity of melatonin at the MT1 and MT2 receptors is believed to contribute to its sleep-promoting properties via their distinct actions on the circadian clock. The MT1 receptors are thought to inhibit neuronal firing, while the MT2 receptors have been implicated in the phase-shifting response.

Rationale for use

Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.

Clinical trials

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 comprised of 5 periods: 1) pre-study period (4 weeks); 2) baseline single-blind placebo period (2 weeks); 3) randomised placebo-controlled treatment period (13 weeks); 4) open label treatment period (91 weeks); and 5) single blind run-out period (2 weeks placebo).

All patients were randomised to either 2 mg of SLENYTO or matching placebo. At the end of first 3 weeks double-blind period and first 13 weeks open-label period, the dose was increased from 2 mg to 5 mg or from 5 mg to 10 mg, when necessary in accordance with the study criteria: absence of serious adverse events and daytime fatigue related to study treatment, compliance with the Sleep and Nap Diary (SND) and study treatment, the patient had ≤6 hours of continuous sleep and/or ≥0.5 hours of sleep latency from light off in≥3 out of 5 nights or the patient had ≤6 hours of continuous sleep and/or ≥0.5 hours of sleep latency from light off only in ≤2 out of 5 nights and did not improve from baseline by at least 1 hour as measured by either shortening of sleep latency or increase in sleep duration or both. Dose reduction was permitted at any time if the patient experienced an adverse event related to study treatment (in particular an unacceptable increase in daytime fatigue or change in behaviour) or if a patient ceased to respond to study treatment (i,e. sleep improved on the initial dose and then deteriorated on a higher dose).

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 randomised and 112 weeks' results are available. Of the study participants, 28.8% patients were diagnosed with Attention deficit hyperactivity disorder (ADHD) before study initiation and 77% had abnormal Strength and Difficulties Questionnaire (SDQ) hyperactivity/inattention score (>=7) at baseline. The baseline demographics and clinical characteristics are summarised in Table 2.

Table 2: Baseline demographics and clinical characteristics at screening for the randomised set

	Randomised set		
Characteristic	**SLENYTO (n=60)**	**Placebo (n=65)**	**Overall (n=125)**
Age (years) Mean ± SD (range)	9.0 ± 4.08 (2, 17)	8.4 ± 4.24 (2, 17)	8.7 ± 4.15 (2, 17)
Gender Male (%) Female (%)	 45 (75%) 15 (25.0%)	 47 (72.3%) 18 (27.7%)	 92 (73.6%) 33 (26.4%)
Diagnoses ASD SMS	 58 (96.7%) 2 (3.3%)	 63 (96.9%) 2 (3.1%)	 121 (96.8%) 4 (3.2%)
Comorbidities ADHD Epilepsy	 16 (26.7%) 10 (16.7%)	 20 (30.8%) 6 (9.2%)	 36 (28.8%) 16 (12.8%)

Randomised 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, the adjusted change from baseline in TST was 51.03 minutes with SLENYTO and 18.71 minutes with placebo. The adjusted mean treatment difference was 32.32 minutes in the Full Analysis Set (FAS) (p=0.035, Table 3).

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, the adjusted change from baseline in SL was -37.77 minutes with SLENYTO and -12.57 minutes with placebo. The adjusted mean treatment difference was -25.2 minutes in the FAS (p=0.011, Table 3) 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 higher with SLENYTO than with placebo (68.9% versus 39.3% respectively).

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. The treatment effects on sleep variables were associated with improved parents' well-being measured by the WHO-5 well-being Index and parents' satisfaction in child sleep pattern measured by the Composite Sleep Disturbance Index (CSDI) (Table 3).

There was a trend to benefit in favour of SLENYTO for total SDQ score, sleep disturbances score measured by the CSDI and longest sleep episode (LSE, p=0.053). There were no significant differences for duration of wake time, number of awakenings and social functioning between SLENYTO and placebo groups.

Table 3: Summary of primary and clinical relevant secondary study outcomes after 13 weeks of double blind period (full analysis set)

Variable	Group	Change from baseline± SD	Adjusted change from baseline (SE) [95% CI]	Treatment difference (SE)	95% CI	p-value*
			Sleep and Nap Diary			
TST	Slenyto	57.36 ± 107.35	51.03 (10.456) [30.30, 71.76]	32.32 (15.100)	2.38, 62.26	0.035
	Placebo	9.14 ± 80.27	18.71 (10.816) [-2.73, 40.15]			
SL	Slenyto	-39.46 ± 60.41	-37.77(6.816) [-51.28, -24.25]	-25.20 (9.787)	-44.61, -5.80	0.011
	Placebo	-12.51 ± 49.19	-12.57 (7.005) [-26.45, 1.32]			
			SDQ			
Externalizing behaviours	Slenyto	-0.7 ± 1.93	-0.70 (0.244)[-1.19;-0.22]	-0.83 (0.355)	-1.54, -0.13	0.021
	Placebo	0.1 ± 1.69	0.13(0.258)[-0.38; 0.64]			
			WHO-5			
WHO-5	Slenyto	1.3 ± 4.96	1.43(0.565)(0.31,2.55)	2.17(0.831)	0.53, 3.82	0.01
	Placebo	-0.5 ±4.27	-0.75(0.608)(-1.95,0.46)			
			CSDI			
CSDI satisfaction	Slenyto	1.4 ± 1.56	1.43(0.175)(1.08,1.78)	0.72(0.254)	0.22, 1.23	0.005
	Placebo	0.8 ±1.19	0.71(0.184)(0.34,1.07)			

TST=Total Sleep Time; SL=Sleep Latency; SDQ = Strength and Difficulties Questionnaire; WHO-5= the World Health Organization Well-Being Index; CSDI = Composite Sleep Disturbance Index; SD = standard deviation; SE = standard Error; *MMRM = mixed-effects model for repeated-measures;

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 104 weeks and 35 completed 91 weeks 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 better than baseline levels with no obvious 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 prolonged release tablets) administration after a standardised 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 melatonin 5 mg (1 x 5 mg 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, 1 mg and 5 mg 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. The binding to the other serum proteins is insignificant. The melatonin binding was constant over the range of the studied concentrations in serum. Literature data indicates that melatonin is distributed in all body fluids and is accessible at all tissues.

Metabolism

Melatonin undergoes a fast first hepatic pass metabolism and is metabolised predominantly by CYP1A enzymes, and possibly CYP2C19 of the cytochrome P450 system with an elimination half life of ca 40 minutes.Prepubertal children and young adults metabolise 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-sulphatoxy-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.

Excretion

Terminal half life (t½) 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 sulphated and glucoronide conjugates of 6-hydroxymeltonin and 2% is excreted as melatonin (unchanged drug).

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.

Renal impairment

There is no experience of the use of melatonin in paediatric patients with renal impairment. 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 (see Section 4.2 Dose and method of administration).

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 adult 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 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Results from a standard battery of *in vitro* and *in vivo* assays showed no evidence of a genotoxic potential for melatonin.

Carcinogenicity

An oral lifetime carcinogenicity study with melatonin in rats showed an increased incidence of thyroid follicular cell adenomas in males at doses around 700-fold the clinical dose of 2 mg in adults, based on body surface area. No neoplastic tissue histopathology was examined at lower doses and therefore the no-effect dose could not be determined. These effects were associated with liver enzyme induction in this species and are unlikely to be relevant to humans.

Oral administration of melatonin for 26 consecutive weeks to hemizygous Tg.rasH2 mice was not carcinogenic up to the tested dose levels of 180 mg/kg body weight, around 400 times the clinical dose of 2 mg in adults.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SLENYTO 1 mg prolonged release tablet:

- ammonio methacrylate copolymer
- calcium hydrogen phosphate dihydrate
- lactose monohydrate
- colloidal anhydrous silica
- purified talc
- magnesium stearate
- Opaglos 2 High Gloss Film Coating System 97W240002 Pink (film coating)

SLENYTO 5 mg prolonged release tablet:

- ammonio methacrylate copolymer
- calcium hydrogen phosphate dihydrate
- lactose monohydrate
- colloidal anhydrous silica
- magnesium stearate
- Opaglos 2 High Gloss Film Coating System 97W220004 Yellow (film coating)

6.2 INCOMPATIBILITIES

Refer to Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

SLENYTO 1 mg tablets: Blister packs (PVC/PVDC/Al) of 30 or 60 tablets.

SLENYTO 5 mg tablets: Blister packs (PVC/PVDC/Al) of 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

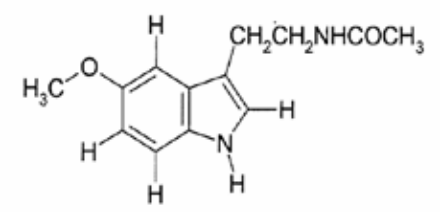
6.7 PHYSICOCHEMICAL PROPERTIES

Melatonin is a slightly off-white, odourless crystalline powder. Melatonin is very slightly soluble in water and in dilute hydrochloric acid.

Chemical structure

Chemical name: N-[2-(5-Methoxyindol-3-yl)ethyl]acetamide.

Structural formula:



Molecular formula: $C_{13}H_{16}N_2O_2$

Molecular weight: 232.27

pKa: 12.3 - 12.7

CAS number

73-31-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine

8 SPONSOR

Sponsor:
RAD Data Australia Pty Ltd
PKF Melbourne
Level 12, 440 Collins Street
Melbourne, VIC, 3000

Distributor:
Aspen Pharma Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065

9 DATE OF FIRST APPROVAL

22 May 2020

10 DATE OF REVISION

N/A

SLENYTO is a registered trademark of Neurim Pharmaceuticals

Summary table of changes

Section changed	Summary of new information
All	New PI for paediatric indication.