

Product Monograph
Including Patient Medication Information

Pr SLENYTO™

Melatonin extended-release tablets

For oral use

1 mg and 5 mg of melatonin

Melatonin receptor agonist

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Recent Major Label Changes

None at the time of the most recent authorization.

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

SLENYTO™ (melatonin extended-release tablets) is indicated for:

- the treatment of insomnia in children and adolescents aged 2 to <18 years with autism spectrum disorder (ASD) and / or Smith-Magenis syndrome (SMS), where sleep hygiene measures have been insufficient.

1.1. Pediatrics

Pediatrics (<2 years): 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 (see [7.1.3 Pediatrics](#)). Therefore, Health Canada has not authorized an indication in this patient population.

1.2. Geriatrics

Melatonin is authorized as a natural health product for use in adults, including geriatrics (see [7.1.4 Geriatrics](#)).

2. Contraindications

SLENYTO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 Dosage Forms, Strengths, Composition, and Packaging](#).

4. Dosage and Administration

4.1. Dosing Considerations

- Data from the clinical pediatric study have shown that body weight and age were weak predictors of the optimal dose. Individual titration is recommended.
- SLENYTO contains lactose and should not be taken by patients with conditions that impact the body's ability to digest or absorb galactose/lactose (see 7.1 Warnings and Precautions, Endocrine and Metabolism, [Lactose](#)).

4.2. Recommended Dose and Dosage Adjustment

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.

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.

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 (see 10.3 Pharmacokinetics, Special Populations and Conditions, [Renal Insufficiency](#)).

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 10.3 Pharmacokinetics, Special Populations and Conditions, [Hepatic Insufficiency](#)).

Pediatric 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 (see [7.1.3 Pediatrics](#)). Health Canada has not authorized an indication in this patient population.

4.2.1. Discontinuing Treatment

There are no known discontinuation effects after stopping treatment with SLENYTO. Following a 91-week treatment period, a 2-week run-out period on placebo showed no signs of withdrawal symptoms or worsening of insomnia.

4.4. Administration

- SLENYTO should be taken once daily, 30 to 60 minutes before bedtime.
- SLENYTO should be taken with or after food.

Method of administration

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

Tablets can be put into food such as yogurt, 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.

4.5. Missed Dose

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.

5. Overdose

SLENYTO has been administered at up to 10 mg daily doses in the pediatric clinical trial over 18 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.

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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
oral	extended-release tablets, 1 mg and 5 mg	<p>SLENYTO 1 mg: Tablet core ammonio methacrylate copolymer type B, dibasic calcium phosphate dihydrate, lactose monohydrate, magnesium stearate, silicon dioxide, talc Film coating of SLENYTO 1 mg: carboxymethylcellulose sodium, dextrose monohydrate, ferric oxide red, ferric oxide yellow, lecithin soybean, maltodextrin, titanium dioxide</p> <p>SLENYTO 5 mg: Tablet core ammonio methacrylate copolymer type A, dibasic calcium phosphate dihydrate, lactose monohydrate, magnesium stearate, silicon dioxide Film coating of SLENYTO 5 mg: carboxymethylcellulose sodium, dextrose monohydrate, ferric oxide yellow, lecithin soybean, maltodextrin, titanium dioxide</p>

Description

1 mg extended-release tablets

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

Container closure system: PVC/PVDC opaque blister with aluminium foil backing.

Pack size: 30 or 60 tablets.

5 mg extended-release tablets

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

Container closure system: PVC/PVDC opaque blister with aluminium foil backing.

Pack size: 30 tablets.

7. Warnings and Precautions

General

Interactions with alcohol and other CNS Depressants

Concomitant use with alcohol, benzodiazepines and non-benzodiazepine hypnotics, opioids, antihistamines, certain antidepressants such as fluvoxamine, imipramine or amitriptyline, cannabis or other drugs that depress the central nervous system is not recommended (see [9.4 Drug-Drug Interactions](#) and [9.3 Drug-Behaviour Interactions](#)). Increased sedation, impaired cognitive function and/or other additive effects may be observed.

Carcinogenesis and Genotoxicity

See 16 Non-Clinical Toxicology, [Carcinogenicity](#).

Dependence, Tolerance and/or Abuse Liability

In clinical studies of up to 104 weeks, no evidence of tolerance or dependence was observed following a 2-week run-out period. No evidence of rebound insomnia was observed after short or long-term use.

Driving and Operating Machinery

Melatonin may cause drowsiness; therefore, may impair performance of a task requiring attention, physical coordination, or unimpaired reaction times and decision-making, including driving and operating machinery. In pediatrics, this may include the use of bicycles and scooters, including electric transportation devices.

Melatonin should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

Endocrine and Metabolism

Lactose

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

Immune

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.

Neurologic

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 comorbid 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. SLENYTO should be used

with caution if the effects of drowsiness are likely to be associated with a risk to safety (see 7 Warnings and Precautions, [Driving and Operating Machinery](#)).

Reproductive Health

- **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 700-fold the maximum recommended human dose (MRHD) of 10 mg in children and adolescents, based on AUC exposure (see 16 Non-Clinical Toxicology, [Reproductive and developmental toxicology](#)).

7.1. Special Populations

7.1.1. Pregnancy

There are no data from the use of melatonin in pregnant women, however, data in animals indicate maternal transfer of melatonin to the fetus via the placenta.

No significant effects on embryofetal development were observed in rats given oral melatonin during the period of organogenesis at doses over 700-fold the MRHD of 10 mg in children and adolescents, based on the AUC exposure (see 16 Non-Clinical Toxicology, [Reproductive and developmental toxicology](#)). As a precautionary measure, melatonin use during pregnancy should be avoided.

7.1.2. Breastfeeding

Endogenous melatonin was measured in human breast milk thus exogenous melatonin is likely secreted into human milk. Data in animals indicate maternal transfer of melatonin to the fetus via the milk. The effect of melatonin on nursing newborns/infants is unknown. Therefore, breastfeeding is not recommended in patients under treatment with melatonin.

7.1.3. Pediatrics

Pediatrics (<2 years): 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.

7.1.4. Geriatrics

SLENYTO is indicated for the pediatric population (aged 2 to <18 years) for the treatment of insomnia in children and adolescents with autism spectrum disorder (ASD) and / or Smith-Magenis syndrome (SMS) only. Melatonin is authorized as a natural health product for use in adults, including geriatrics.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most frequently reported treatment-emergent adverse events (reported in $\geq 10\%$ of patients) in clinical studies with SLENYTO were somnolence, fatigue, mood swings, headache, upper respiratory tract infection, vomiting, agitation, cough, dyspnea and rash.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

See [8.2.1 Clinical Trial Adverse Reactions - Pediatrics](#).

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

The pediatric studies for SLENYTO comprised one Phase 3 safety and efficacy study and one pharmacokinetic study, with safety data of up to 104 weeks of treatment. In the Phase 3 study, 125 patients diagnosed with ASD (121 patients) or SMS (4 patients), aged 2 to <18 years, were randomized to receive SLENYTO (N = 60) or placebo (N = 65) during a 13-week double-blind period before entering a 91-week open-label period in which all patients were treated with SLENYTO.

Table 2 presents the treatment-emergent adverse events (≥5%) reported in the study, regardless of causality.

Table 2 – Treatment-Emergent Adverse Events Observed in ≥5% of Patients with ASD or SMS Treated with SLENYTO in Study NEU_CH_7911*

System organ class / preferred term	13-Week Double-blind Period		91-Week Open-label Period
	SLENYTO N=60 n (%)	Placebo N=65 n (%)	SLENYTO N=95 n (%)
Gastrointestinal Disorders			
Vomiting	8 (13.3)	10 (15.4)	20 (21.1)
Nausea	4 (6.7)	1 (1.5)	9 (9.5)
Constipation	3 (5.0)	1 (1.5)	8 (8.4)
Diarrhea	3 (5.0)	3 (4.6)	3 (3.2)
General Disorders and Administration Site Conditions			
Fatigue	15 (25.0)	12 (18.5)	25 (26.3)
Pyrexia	5 (8.3)	4 (6.2)	7 (7.4)
Hangover	3 (5.0)	3 (4.6)	7 (7.4)
Infections and Infestations			
Upper respiratory tract infection	9 (15.0)	7 (10.8)	14 (14.7)
Otitis media	5 (8.3)	3 (4.6)	7 (7.4)
Nasopharyngitis	4 (6.7)	1 (1.5)	6 (6.3)
Influenza	-	-	8 (8.4)
Gastroenteritis	-	-	6 (6.3)
Sinusitis	-	-	5 (5.3)
Nervous System Disorders			
Somnolence	17 (28.3)	8 (12.3)	24 (25.3)
Headache	8 (13.3)	4 (6.2)	12 (12.6)
Dizziness	-	-	6 (6.3)

System organ class / preferred term	13-Week Double-blind Period		91-Week Open-label Period
	SLENYTO N=60 n (%)	Placebo N=65 n (%)	SLENYTO N=95 n (%)
Psychiatric Disorders			
Agitation	11 (18.3)	7 (10.8)	8 (8.4)
Mood swings	10 (16.7)	11 (16.9)	17 (17.9)
Anxiety	-	-	6 (6.3)
Aggression	-	-	5 (5.3)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	7 (11.7)	5 (7.7)	16 (16.8)
Dyspnea	6 (10.0)	4 (6.2)	10 (10.5)
Asthma	-	-	6 (6.3)
Rhinorrhea	-	-	5 (5.3)
Skin and Subcutaneous Tissue Disorders			
Rash	3 (5.0)	3 (4.6)	10 (10.5)

*Study Dose and Duration: Double-Blind (DB) Period: Randomized patients received SLENYTO 2 mg or placebo. After 3 weeks of DB treatment, dose modification to 5 mg was allowed in a DB manner for the remaining 10 weeks of the 13-week DB Period. Open-Label (OL) Period: Patients receiving SLENYTO in the DB Period continued their dose for 13 weeks. Patients on placebo in the DB Period, received SLENYTO 2 mg for 13 weeks. After 13 weeks in the OL Period, dose adjustment occurred (dose could be increased to 5 mg for those on 2 mg and to 10 mg for those on 5 mg). The adjusted dose was maintained for the duration of the OL Period (78 weeks) for a total OL Period duration of 91 weeks.

ASD = Autism spectrum disorder; SMS = Smith-Magenis syndrome

During the double-blind phase, treatment-related adverse events (AEs) were reported by 12 (20.0%) patients (28 events) in the SLENYTO group and 11 (16.9%) patients (17 events) in the placebo group. Somnolence was more commonly reported as a treatment-related adverse event in the SLENYTO group (11.7%) compared to placebo (3.1%), whereas fatigue and mood swings were more commonly reported as treatment-related AEs in the placebo group compared to SLENYTO (4.6% vs 3.3% and 6.2% vs 1.7%, respectively).

There were no serious adverse events in the SLENYTO group during the double-blind phase.

During the double-blind phase, one patient in the SLENYTO group permanently discontinued the study due to fatigue, agitation, and stereotypy; all events were non-serious.

Adverse events with a possible or probable relationship with single-dose administration of SLENYTO 2 x 1 mg and 10 x 1 mg from the pharmacokinetic study in children with neurodevelopmental disorders and sleep disturbances included fatigue, sensation of heaviness, somnolence, falling asleep, headache, and nausea. Nausea, fatigue and headache were more frequently reported following SLENYTO 10 mg compared with SLENYTO 2 mg dose.

8.3. Less Common Clinical Trial Adverse Reactions

8.3.1. Less Common Clinical Trial Adverse Reactions – Pediatrics

The following treatment-related adverse events were observed in the pharmacokinetic study and/or in the Phase 3 safety and efficacy study:

Gastrointestinal disorders: abdominal pain upper, hematochezia

Investigations: urine output decreased

Nervous system disorders: increased excitability, psychomotor hyperactivity, sudden onset of sleep

Psychiatric disorders: enuresis, inappropriate affect, irritability, middle insomnia, stereotypy

Respiratory, thoracic and mediastinal disorders: sinusitis

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

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

8.5. Post-Market Adverse Reactions

The following adverse reactions (frequency unknown) have been reported in pediatrics with off-label use of an adult formulation of extended-release melatonin tablets (similar to SLENYTO): epilepsy, visual impairment, dyspnea, epistaxis, constipation, decreased appetite, swelling face, skin lesion, feeling abnormal, abnormal behaviour and neutropenia.

Furthermore, in children with ASD and neurogenetic disorders 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 $\geq 0.1\%$ to $<1\%$) have been reported: depression, nightmares, drowsiness, hyperphagia, panic attacks, nocturnal awakenings, dry mouth, phobia, halitosis and tachycardia.

9. Drug Interactions

9.2. Drug Interactions Overview

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 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 (see [9.4 Drug-Drug Interactions](#)).

Melatonin has been observed to induce CYP3A in vitro at supratherapeutic concentrations. The clinical

relevance of this finding is unknown. If induction occurs, plasma concentrations of concomitantly administered drugs can be reduced.

9.3. Drug-Behaviour Interactions

Smoking

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

Alcohol

Alcohol should be avoided, including medicines containing alcohol (e.g., cough medicines). Alcohol inhibits the secretion of endogenous melatonin, thereby reducing its effectiveness on sleep. Additionally, alcohol affects the dissolution profile of SLENYTO in vitro, therefore the prolonged release characteristics of SLENYTO may be altered, resulting in immediate release of melatonin.

Cannabis

Cannabis and other recreational sedative substances should be avoided with melatonin use as synergistic or counteracting effects may occur.

9.4. Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction studies or potential interactions and included due to the expected magnitude and seriousness of the interaction.

Table 3 – Established or Potential Drug-Drug Interactions

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Beta-blockers	T	PK interaction - Plasma concentration of melatonin may be decreased. Beta-blockers may suppress the night-time release of endogenous melatonin.	If possible, administration of beta-blockers should be in the morning.
Carbamazepine and rifampicin	T	PK interaction - Plasma concentration of melatonin may be decreased by CYP1A2 inducers.	Review / increase dose of melatonin.
Cimetidine	CT	PK interaction - Cimetidine is a potent inhibitor of certain cytochrome P450 (CYP450) enzymes, mainly CYP1A2, and thereby increases plasma melatonin levels by inhibiting its metabolism. Plasma concentration of melatonin significantly increased mean melatonin C _{max} and AUC, but there was no effect on PD response. There was no effect on the PK of cimetidine.	Review / reduce dose of melatonin.

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Ciprofloxacin and other quinolones	T	PK interaction - Plasma concentration of melatonin may be increased by CYP1A2 inhibitors.	Monitor. Review / reduce dose of melatonin if prescribed long-term.
Estrogens	T	PK interaction - Estrogens (e.g., contraceptive or hormone replacement therapy) can increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2. Plasma concentration of melatonin may be increased.	Review / reduce dose of melatonin.
Fluvoxamine	T	PK interaction - Plasma concentration of melatonin significantly increased (17-fold higher AUC and 12-fold higher serum C_{max}) by inhibiting its metabolism by CYP1A2 and CYP2C19.	The combination should be avoided.
Imipramine	CT	No clinically significant PK interaction. However, melatonin co-administration resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone.	The combination should be avoided.
Benzodiazepines/ non- benzodiazepine hypnotics	CT	PD interaction - Increased impairment of attention, memory, and coordination, particularly 1-hour post-dosing. Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a CT, there was clear evidence for a transitory PD interaction between melatonin and zolpidem one hour following co-dosing.	Combination with benzodiazepines and non-benzodiazepine hypnotics should be avoided.

Legend: CT = Clinical Trial; T = Theoretical

9.5. Drug-Food Interactions

Following administration of a single 5 mg dose of SLENYTO under high-fat, high-calorie fed conditions to healthy adult subjects, C_{max} and AUC_T were increased by 2-fold and 1.2-fold, respectively, as compared to administration under fasted conditions (see [10.3 Pharmacokinetics](#)). Under fed conditions, T_{max} was also delayed by approximately 1 hour as compared to a fasted state. SLENYTO

should be administered with or after food (see [4.4 Administration](#)).

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. 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.

10.2. Pharmacodynamics

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 a.m. 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.

10.3. Pharmacokinetics

Table 4 – Summary of Melatonin Extended-release Tablets Pharmacokinetic Parameters^a in Children with ASD and Healthy Adults

Single Dose Mean	C _{max} (pg/mL)	T _{max} (h)	t _½ (h)	AUC _{0-∞} (ng·h/mL)	CL (L/h)	Vd (L)
2 mg ^b (2 x 1 mg)	410	2	4.9	2.2	1110	7980
1 mg ^c	620	2.3	1.6	2.1	639.1	1551.9
5 mg ^c	3570	3.1	1.3	10.99	788.1	1330.4

^a fed condition; ^b pediatric population in saliva; ^c adult population in plasma

Absorption

In the pediatric population comprising 16 children with ASD, ages 7-15 years old, suffering from insomnia, following SLENYTO 2 mg (2 x 1 mg 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 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), T_{max} was earlier (within 2 hours), and AUC_T was slightly

reduced (-16%) as compared to a fed state.

The C_{max} , $AUC_{0-\infty}$, and AUC_{0-last} measured in saliva and plasma samples following a single dose of SLENYTO 1 mg in adults showed a positive correlation with Spearman correlation coefficients of 0.660 (C_{max}), 0.929 ($AUC_{0-\infty}$) and 0.825 (AUC_{0-last}), indicating that saliva melatonin concentrations may substitute for plasma melatonin concentrations in children.

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 extended-release melatonin tablets and data with 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, alpha₁-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 metabolized predominantly by CYP1A enzymes, and possibly CYP2C19 of the cytochrome P450 system with elimination half-life of approximately 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-SMT), 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 ($t_{1/2}$) 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 glucuronic acid and excreted in the urine as their corresponding 6-sulfatoxy and 6-glucuronide derivatives.

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

Special populations and conditions

- **Pediatrics:** High variability in pharmacokinetics after oral melatonin intake is documented in literature and may result from small differences in the rapid first hepatic pass metabolism. Data from a pediatric PK study with SLENYTO suggests that variability overrides any PK differences

that may exist due to age weight or pubertal stage.

- **Sex:** 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.
- **Hepatic Insufficiency:** 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 pediatric 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 4.2 Recommended Dose and Dosage Adjustment, Special Populations, [Hepatic impairment](#)).
- **Renal Insufficiency:** There is no experience of the use of melatonin in pediatric patients with renal impairment (see 4.2 Recommended Dose and Dosage Adjustment, Special Populations, [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.

11. Storage, Stability, and Disposal

Store at room temperature (15°C to 30°C) in a cool dry place away from moisture, heat or sunlight.

SLENYTO tablets should be kept in its original blister package.

Keep out of the reach and sight of children.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance(s): melatonin

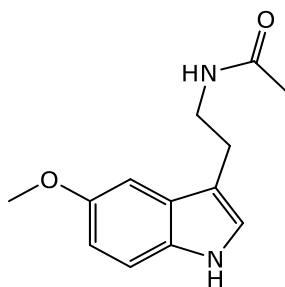
Chemical name: N-[2-(5-Methoxyindol-3-yl)ethyl]acetamide (Ph.Eur.)

N-Acetyl-5-methoxytryptamine (USP)

Molecular formula and molecular mass: $C_{13}H_{16}N_2O_2$

232.28

Structural formula:



Physicochemical properties: Melatonin is a white to off-white, odourless crystalline powder.
Melatonin is very slightly soluble in aqueous solution at pH 1.0 to 10.0.

14. Clinical Trials

14.1. Clinical Trials by Indication

Insomnia in children and adolescents aged 2 to <18 years with ASD and / or SMS

Table 5 – Summary of Patient Demographics for Clinical Trials in Children Diagnosed with ASDs and Neurodevelopmental Disabilities Caused by SMS

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
NEU_CH_7911	Phase 3, Randomized, placebo-controlled study	<u>Double-blind:</u> 2 or 5 mg, oral 13 weeks	<u>SLENYTO:</u> n=60 <u>Placebo:</u> n=65 (Total subjects: n=125)	<u>SLENYTO:</u> 9.0 (2 to <18) years <u>Placebo:</u> 8.4 (2 to <18) years	<u>SLENYTO:</u> Male: 45 (75.0%) Female: 15 (25.0%) <u>Placebo:</u> Male: 47 (72.3%) Female: 18 (27.7%)
		<u>Open-label extension:</u> 2 or 5 mg, oral 13 weeks 2, 5 or 10 mg, oral >13 to 78 weeks (Total open-label: 91 weeks)	N=95		

Efficacy and safety have been assessed in a Phase 3, randomized, placebo-controlled study in children diagnosed with ASDs (n = 121) and neurodevelopmental disabilities caused by SMS (n = 4) who had not shown improvement after standard sleep behavioural intervention. Treatment was administered for up to two years.

The study comprised 5 periods: 1) pre-study period (4 weeks), 2) baseline single-blind run-in placebo period (2 weeks), 3) randomized, placebo-controlled, double-blind 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 the first 3 weeks double-blind period and/or first 13 weeks open-label period, the dose could be 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).

The primary endpoint was total sleep time (TST). Key secondary endpoints included sleep latency (SL) and longest sleep episode (LSE). Additional analyses included behavior at home and in school as assessed by the Strength and Difficulties Questionnaire (SDQ).

A total of 125 children (2 to <18 years of age, mean age 8.7 ± 4.15 ; 96.8% ASD, 3.2% SMS) whose sleep failed to improve on behavioural intervention alone were randomized and 104 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 SDQ hyperactivity/inattention score (≥ 7) at baseline. The clinical characteristics are summarised in Table 6.

Table 6 – Clinical Characteristics at Screening for the All Randomised Set

Characteristic	All Randomized Set		
	SLENYTO (n=60)	Placebo (n=65)	Overall (n=125)
Diagnosis			
ASD	58 (96.7%)	63 (96.9%)	121 (96.8%)
SMS	2 (3.3%)	2 (3.1%)	4 (3.2%)
Comorbidities			
ADHD	16 (26.7%)	20 (30.8%)	36 (28.8%)
Epilepsy	10 (16.7%)	6 (9.2%)	16 (12.8%)

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 TST after 13 weeks of double-blind treatment. At baseline, mean TST was 507.8 minutes in the SLENYTO and 487.9 minutes in the placebo group. After 13 weeks of double-blind treatment, participants slept on average 57.4 minutes longer at night with SLENYTO compared to 9.1 minutes with placebo. The adjusted mean treatment difference between SLENYTO and placebo was 32.3 minutes in the Full Analysis Set; MMRM ($p=0.035$).

At baseline, mean SL was 95.2 minutes in the SLENYTO group and 98.8 minutes in the placebo group. By the end of the 13-week treatment period, children fell asleep on average 39.5 minutes faster with SLENYTO and 12.5 minutes faster with placebo. The adjusted mean treatment difference between SLENYTO and placebo was -25.2 minutes in the Full Analysis Set; MMRM ($p=0.011$) without causing earlier wake up time.

Besides shortening of SL, an increase in the 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 77.7 minutes in the SLENYTO-treated group, compared to 25.5 minutes in the placebo-treated group. The adjusted estimated treatment difference was 42 minutes in the Full Analysis Set (MMRM, $p=0.053$).

Wake up time was unaffected; after 13 weeks, patients' wake up time was delayed insignificantly by 0.09 hour (5.4 minutes) with SLENYTO compared to placebo treatment.

Table 7 – Change from Baseline (minutes) after 13 Weeks of Double-Blind Treatment in Patients with ASD or SMS in Study NEU_CH_7911 (FAS)

	SLENYTO (N = 58)	Placebo (N = 61)	Treatment difference (SE) [95% CI] p-value
	Adjusted treatment means (SE)		
Primary endpoint			
TST	51.03 (10.456)	18.71 (10.816)	32.32 (15.100) [2.38, 62.26] 0.035
Key secondary endpoints			
SL	-37.77 (6.816)	-12.57 (7.005)	-25.20 (9.787) [-44.61, -5.80] 0.011
LSE	71.99 (14.763)	30.01 (15.492)	41.98 (21.431) [-0.57, 84.53] 0.053

Analysis conducted on the Full Analysis Set using a MMRM model with the value at Week 5 (3 weeks of double-blind [DB] treatment) and Week 15 (13-weeks of DB treatment) as the dependent variable, with fixed effects for visit, the mean baseline value, randomized treatment and the mean baseline value and randomized treatment both nested within visit.

ASD = Autism spectrum disorder; CI = Confidence interval; FAS = Full Analysis Set; LSE = Longest sleep episode; MMRM = Mixed-effects model for repeated-measures; SE = Standard error; SL= Sleep latency; SMS = Smith-Magenis syndrome; TST = Total sleep time

SLENYTO 2 mg/5 mg treatment also resulted in improvement over placebo in the child's externalizing behaviours (hyperactivity/inattention+ conduct scores) as assessed by the SDQ after 13 weeks of double-blind treatment.

Open-label treatment period results (91 weeks)

Patients (51 from the SLENYTO group and 44 from the placebo group, mean age 9 ± 4.24 years, range 2-17 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 in the study, 39 patients originally randomized to SLENYTO completed 13 weeks of the double-blind phase and 91 weeks of the open-label treatment period (i.e., 104 weeks of SLENYTO treatment) and 35 patients originally randomized to placebo completed 13 weeks of the double-blind phase on placebo and 91 weeks of the open-label period of SLENYTO treatment. The improvements in TST, SL and duration of uninterrupted sleep (LSE) 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.

16. Non-Clinical Toxicology

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

General toxicology

In the chronic oral (gavage) repeat dose study in adult rats at melatonin dose levels ranging from 15 to 150 mg/kg/day for 13 or 26 weeks, melatonin was associated with minor post dose signs, including cage-tray observations, and slight increases in food consumption and body weight in males from the high-dose group. These findings were reversible during the 4-week treatment-free period. None of these findings were considered to be adverse. The liver showed centrilobular hypertrophy in half of the high-dose males, but the liver was identified as an organ of histopathological adaptive change. Therefore, the no observed adverse effect level (NOAEL) in rats following 26 weeks of oral administration was identified as 150 mg/kg/day, with a corresponding exposure (AUC) of 25654 ng.h/mL that is 621-fold the maximum recommended human dose (MRHD) of 10 mg in children and adolescents.

Following chronic oral administration (gavage) in pre-pubertal dogs, no melatonin-related changes were observed at the maximum dose tested of 8 mg/kg/day (NOAEL). AUC at this dose was 3424 ng.h/mL, which represented a safety margin of 83-fold the MRHD.

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 carcinogenicity study with melatonin in rats showed an increased incidence of thyroid follicular cell adenomas in males at the dose of 150 mg/kg/day, that is 621-fold the MRHD based on an AUC of 25654 ng.h/mL. No neoplastic tissue histopathology was examined at lower doses and therefore the no-effect dose could not be determined. Occurrence of thyroid adenomas 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 713 times the MRHD of 10 mg in children and adolescents, based on an AUC of 29450 ng.h/mL.

Reproductive and developmental toxicology

In the fertility and early embryonic development study in rats, there was evidence of taste aversion at melatonin doses given by oral gavage of 200 mg/kg/day and to a lesser extent at 55 mg/kg/day, but there was no evidence of overt toxicity in the form of body weight change, food intake or macroscopic necropsy findings, except for two occurrences (out of 24 animals) of cysts in the ovary at the high dose of 200 mg/kg/day. There were no effects on mating performance, fertility or embryo survival (post-implantation loss) up to Day 13 of gestation at dose levels up to 200 mg/kg/day, but pre-implantation loss was slightly increased at this dose level. Semiology showed no effects.

In a definitive embryo-fetal development study in pregnant Sprague-Dawley rats, mild maternal toxicity (taste aversion, lethargy and a reduction in body weight gain) was observed at melatonin doses ≥ 100 mg/kg/day, but no embryo-fetal abnormalities were observed at any dose tested (up to 200 mg/kg/day by gavage). The no observed effect level (NOEL) for maternal toxicity was therefore considered to be 10 mg/kg/day. In pregnant New Zealand White rabbits, no maternal toxicity, teratogenicity, embryo lethality, or embryo-retardation effects were noted at any melatonin dose tested (up to 150 mg/kg/day by gavage). Based on these results, NOAELs for embryo-fetal development

were concluded to be 200 mg/kg/day in rats and 150 mg/kg/day in rabbits.

In Sprague Dawley rats, pre- and postnatal development to weaning was unaffected by treatment at melatonin dose levels up to 55 mg/kg/day (by gavage). At 200 mg/kg/day, excess salivation and forelimbs paddling were reported but there were no effects on parturition, the number of offspring born or their initial postnatal development, however, during the last week of lactation, offspring growth and survival was slightly less than that of the controls. There was some evidence of slightly delayed maturity (e.g., vaginal opening) in all treatment groups at weaning but there were no effects on the subsequent physical, functional and sexual development of the F1 generation.

Juvenile toxicity

In a repeat dose, 70-day toxicity study in juvenile rats (23-26 days old at start of treatment with 20, 80 or 160 mg/kg/day by oral gavage), mortality, clinical signs, body weight, estrous cyclicity, sexual maturity, sperm parameters and macroscopic findings were unaffected. A reversible increase in reticulocyte count and total bilirubin was observed in females at 160 mg/kg/day and a reversible increase in liver weight was noted in males dosed at ≥ 80 mg/kg/day and in females at 160 mg/kg/day. A non-reversible increase in splenic weight was also seen in females receiving 160 mg/kg/day. Non-reversible, minimal extramedullary hematopoiesis in the spleen was observed in females dosed at 160 mg/kg/day. The NOAEL was considered to be 80 mg/kg/day which corresponded to an AUC of 22150 ng.h/mL representing a safety margin of 536-fold the MRHD.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSLENYTO™

melatonin extended-release tablets

This Patient Medication Information is written for the person who will be taking **SLENYTO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **SLENYTO**, talk to a healthcare professional.

What SLENYTO is used for:

SLENYTO is used to treat sleeping problems (insomnia):

- in children and adolescents aged 2 to less than 18 years of age with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome (SMS); and
- when a healthy sleeping routine (such as regular bedtime and soothing sleeping environment) has not worked well.

How SLENYTO works:

SLENYTO is a medicine that contains the active ingredient melatonin. It is a hormone that regulates the sleep-wake cycle. It is naturally produced by the brain at dusk and during the night. SLENYTO helps reduce the time it takes to fall asleep and improve the time spent sleeping in children and adolescents with ASD and/or SMS who often have difficulty with sleeping.

The ingredients in SLENYTO are:

Medicinal ingredient: melatonin

Non-medicinal ingredients: ammonio methacrylate copolymer type B (1 mg tablets only), ammonio methacrylate copolymer type A (5 mg tablets only), carboxymethylcellulose sodium, dextrose monohydrate, dibasic calcium phosphate dihydrate, ferric oxide red (1 mg tablets only), ferric oxide yellow, lactose monohydrate, lecithin soybean, magnesium stearate, maltodextrin, silicone dioxide, talc (1 mg tablets only), and titanium dioxide.

SLENYTO comes in the following dosage form:

Extended-release tablets; 1 mg and 5 mg.

Do not use SLENYTO if:

- you are allergic to melatonin or to any of the other ingredients in SLENYTO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SLENYTO. Talk about any health conditions or problems you may have, including if you:

- are taking any other medicines.
- consume alcohol.
- are a smoker.

- have the following rare hereditary conditions:
 - Galactose intolerance
 - Total lactase deficiency
 - Glucose-galactose malabsorption
 SLENYTO contains lactose.
- have an autoimmune disease.
- have liver or kidney problems.
- have attention deficit hyperactivity disorder (ADHD).
- are pregnant, think you might be pregnant or are planning to become pregnant. SLENYTO is not recommended during pregnancy. Tell your healthcare professional **right away** if you discover that you are pregnant during treatment with SLENYTO.
- are breastfeeding or are planning to breastfeed. SLENYTO may pass into breastmilk and affect your breastfed baby. SLENYTO is not recommended while breastfeeding.

Other warnings you should know about:

Driving and using machines: SLENYTO can make you feel drowsy. This may affect your ability to drive, ride a bicycle or scooter, use tools or machinery. Before you do tasks requiring special attention, wait until you know how SLENYTO affects you. If you suffer from continued drowsiness, tell your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SLENYTO:

- cimetidine (used to treat stomach problems such as heartburn and ulcers)
- rifampicin and quinolones such as ciprofloxacin and norfloxacin (used to treat bacterial infections)
- estrogens (used in contraceptives or hormone replacement therapy)
- medicines that can cause drowsiness, slowed breathing or induce sleep such as:
 - alcohol. Avoid drinking alcohol or taking medicines that contain alcohol during treatment with SLENYTO as it reduces its effectiveness.
 - antihistamines (used to treat allergies)
 - opioids (used to relieve pain)
 - benzodiazepines and non-benzodiazepine hypnotics such as zaleplon, zolpidem and zopiclone (used to induce sleep)
 - certain medicines used to treat depression (e.g., imipramine, amitriptyline)
 - fluvoxamine (used to treat depression and obsessive-compulsive disorder)
 - beta-blockers (used to control blood pressure). These medicines should be taken in the morning.
 - carbamazepine (used to treat epilepsy)
 - cannabis or other recreational drugs
- smoking. Tell your healthcare professional if you start or stop smoking during treatment. Your dose of SLENYTO may need to be adjusted.

How to take SLENYTO:

- Always take SLENYTO exactly as your healthcare professional has told you. Ask your healthcare professional if you are unsure.
- SLENYTO should be taken once daily, 30 to 60 minutes before bedtime.
- The tablets should be taken with or after food.
- Swallow tablets whole. Do **NOT** break, crush or chew tablets.
- The whole tablets can be put into food like yogurt, 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.

Usual dose:

- The recommended starting dose is 2 mg (two 1 mg tablets) once daily. If there is no improvement in your symptoms, your healthcare professional may increase the dose of SLENYTO to find the most suitable dose for you.
- The maximum daily dose is 10 mg (two 5 mg tablets).
- You will be monitored regularly (every 6 months) by your healthcare professional. This is to check that SLENYTO is still the right treatment for you.
- Talk to your healthcare professional before you stop taking SLENYTO. It is important to continue taking this medicine to treat the condition.

Overdose:

If you think you, or a person you are caring for, have taken too much SLENYTO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take a dose, take it as soon as you remember, before going to sleep that night. However, if the dose was forgotten after bedtime, skip the missed dose and take the next dose the next evening as usual.

Possible side effects from using SLENYTO:

These are not all the possible side effects you may have when taking SLENYTO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with SLENYTO may include:

- abdominal pain
- bad breath
- bedwetting
- blood in stool
- changes in appetite
- changes in mood
- constantly moving and/or excessive fidgeting, tapping or talking (hyperactivity)
- constipation

- cough
- decreased urination
- depression
- diarrhea
- difficulty returning to sleep
- dizziness
- dry mouth
- ear infection
- feeling irritable, aggressive or agitated
- feeling sleepy and lack of energy during the day, even after adequate sleep
- fever
- hangover feeling
- headache
- inappropriate emotional expression
- increased heartbeat
- irrational fear
- nausea
- nightmares
- repetitive movements, postures or spoken words
- runny nose
- skin rash
- stomach flu
- strong desire for sleep, sleeping for unusually long periods, or falling asleep suddenly
- swelling and inflammation of the sinuses (sinusitis)
- upper respiratory infection
- vomiting

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Allergic reaction: breathlessness/shortness of breath, swelling of tongue, lips and face, difficulty swallowing, skin rash, itching and hives			√
Epistaxis (nosebleed)		√	
Neutropenia (low white blood cell count): infections, fatigue, fever, aches, pains and flu-like symptoms		√	
Seizures (fits): uncontrollable shaking with or without loss of consciousness			√
Vision problems			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store SLENYTO at room temperature (15°C to 30°C).
- Store in a cool dry place away from moisture, heat or sunlight (e.g., do not store it in the bathroom or near a sink, or in the car or on windowsills).
- Keep your tablets in the blister pack until it is time to take them. If you take the tablets out of the blister pack, they may not keep as well.
- Keep out of reach and sight of children.

If you want more information about SLENYTO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); or by calling 1-877-258-3240.

This leaflet was prepared by Neurim Pharmaceuticals Ltd.

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