PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrSILENOR®

doxepin tablets
Tablets, 3 mg and 6 mg doxepin (as doxepin hydrochloride), Oral

Hypnotic agent

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.5 Missed dose	2025-02

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SILENOR (doxepin tablet) is indicated for:

- the treatment and symptomatic relief of insomnia characterized by frequent nocturnal awakening, and/or early morning awakenings.

The clinical trials performed in support of efficacy were up to 1 month duration in adults and 3 months in duration in the elderly (≥ 65 years of age).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): During clinical trials, no overall differences in safety or effectiveness were observed in elderly and adult patients, however greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

SILENOR is contraindicated in patients:

- with known intolerance or hypersensitivity to doxepin hydrochloride, other dibenzoxepine compounds or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- with untreated narrow angle glaucoma.
- with severe urinary retention.
- currently taking monoamine oxidase inhibitors (MAOIs) or who have used MAOIs within the past two weeks. Serious side effects and even death have been reported following the concomitant use of certain drugs with MAOIs.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

SILENOR should be taken within 30 minutes of bedtime. To minimize the potential for next day effects, SILENOR should not be taken within 3 hours of a meal (see 10.3 Pharmacokinetics). If symptoms fail to remit after 7-10 days, alternative primary psychiatric or medical illness should be considered.

4.2 Recommended Dose and Dosage Adjustment

Adults: The recommended dose of SILENOR for adults is 6 mg once daily. A 3 mg once daily dose may be appropriate for some patients, if clinically indicated.

Geriatrics (≥ 65 years old): The recommended starting dose of SILENOR in geriatric patients is 3 mg once daily. The daily dose can be increased to 6 mg, if clinically indicated.

The safety and efficacy of SILENOR in the treatment of insomnia at doses higher than 6 mg has not been established and is therefore not recommended.

Pediatrics (< 18 years of age): SILENOR is not indicated for patients less than 18 years of age.

Use in Patients with Hepatic Impairment: Patients with hepatic impairment may display higher doxepin concentrations than healthy individuals. Initiate SILENOR treatment with 3 mg in patients with hepatic impairment and monitor closely for adverse daytime effects.

4.5 Missed dose

If a dose is missed, the patient should be instructed to take the next dose when it is due. The patient should be instructed to not make up for a missed dose by taking double dose next time.

5 OVERDOSAGE

Doxepin is routinely administrated for indications other than insomnia at doses 10- to 50-fold higher than the highest recommended dose of SILENOR (6 mg).

Symptoms: Excessive drowsiness leading to minor alterations of consciousness and even unresponsiveness could be an early indication of excessive dosage. However, overdosage with doxepin hydrochloride is more likely to be manifested by increased psychomotor agitation and convulsions leading to apnea and coma. The electrocardiogram (ECG) changes (broadening of QRS and T-wave abnormalities) tend to be a late finding and are not always accompanied by cardiovascular hemodynamic changes.

The following adverse effects have been associated with use of doxepin at doses higher than 6 mg.

Anticholinergic Effects: constipation and urinary retention

Central Nervous System: disorientation, hallucinations, numbness, paresthesias, extrapyramidal symptoms, seizures, tardive dyskinesia

Cardiovascular: hypotension

Gastrointestinal: aphthous stomatitis, indigestion

Endocrine: raised libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion

Other: weight gain, sweating, flushing, jaundice, alopecia, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine)

Treatment: In general, treatment of overdosage should be symptomatic and supportive. Cardiac arrhythmias and central nervous system (CNS) involvement pose the greatest threat with tricyclic antidepressant overdosage and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdosage of doxepin hydrochloride, particularly children, should be hospitalized and kept under close surveillance.

If the patient is conscious, induced emesis followed by gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be accomplished as soon as possible. Following lavage, activated charcoal may be administered to reduce absorption. An adequate

airway should be established in comatose patients and assisted ventilation instituted, if necessary. The possibility of occurrence of seizures should be kept in mind. External stimulation should be minimized to reduce the tendency to convulsions. Convulsions, should they occur, may respond to standard anticonvulsant therapy. However, barbiturates should be avoided since they may potentiate respiratory depression, particularly in children, and aggravate hypotension and coma.

ECG monitoring in an intensive care unit is recommended in all patients, particularly in the presence of ECG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal. A patient who has ingested a toxic overdose of a tricyclic antidepressant may remain medically and psychiatrically unstable for several days due to sustained excessive drug levels. Unexpected cardiac deaths have occurred up to 6 days after overdosage with other antidepressants. The QRS interval of the electrocardiogram appears to be a reliable correlate of the severity of overdosage. If the QRS interval exceeds 100 milliseconds any time during the first 24 hours after overdosage, cardiac function should be continuously monitored for 5 or 6 days. Because of its effect on cardiac conduction, digitalis should be used only with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

Shock should be treated with supportive measures such as intravenous fluids, oxygen and corticosteroids. Pressor agents, such as noradrenaline (but not adrenaline), are rarely indicated and should be given only after careful consideration and under continuous monitoring.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the cardiovascular and CNS anticholinergic manifestations of tricyclic overdose. The recommended dosage in adults has been 1 mg to 2 mg in very slow intravenous injection. In children, the initial dosage should not exceed 0.5 mg and should be adjusted to age and response. Since physostigmine has a short duration of action, administration may have to be repeated at 30 to 60 minute intervals.

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered.

For 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, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet, 3 mg and 6 mg of doxepin (supplied as doxepin hydrochloride)	colloidal silicon dioxide, D&C yellow no. 10 aluminum lake (6 mg tablets only), FD&C blue no. 1 aluminum lake, magnesium stearate and microcrystalline cellulose

SILENOR is formulated as an oval shaped tablet available in two strengths, 3 mg and 6 mg, and showing the following distinguishable characteristics:

- 3 mg tablet is blue and identified with debossed markings of “3” on one side and “SP” on the other
- 6 mg tablet is green and identified with debossed markings of “6” on one side and “SP” on the other

SILENOR is supplied in bottles of 30 tablets.

7 WARNINGS AND PRECAUTIONS

General

***CNS depressant effects*:** When taken with SILENOR, the sedative effects of other CNS depressants, sedating antihistamines and alcoholic beverages may be potentiated (see 9.4 Drug-Drug Interactions). Patients should not consume alcohol with SILENOR (see 9.4 Drug-Drug Interactions). Patients should be cautioned about potential additive effects of SILENOR used in combination with CNS depressants or sedating antihistamines.

***Complex sleep-related behaviours*:** Complex behaviours such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a hypnotic, with amnesia for the event) have been reported with hypnotics. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with “sleep-driving”, patients usually do not remember these events. These events can occur in hypnotic-naive as well as in hypnotic-experienced persons. Although behaviours such as “sleep-driving” may occur with hypnotics alone at therapeutic doses, the use of alcohol and other CNS depressants with hypnotics appears to increase the risk of such behaviours, as does the use of hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of SILENOR should be strongly considered for patients who report a “sleep-driving” episode or other complex behaviours episode.

Dependence/Tolerance

Potential withdrawal effects were assessed in a 35-day double blind study of adults with chronic insomnia who were randomized to placebo, SILENOR 3 mg, or SILENOR 6 mg. There was no indication of a withdrawal syndrome after discontinuation of SILENOR treatment (3 mg or 6 mg), as measured by the Tyrer’s Symptom Checklist. Discontinuation-period emergent nausea and vomiting occurred in 5 % of subjects treated with 6 mg SILENOR, versus 0 % in 3 mg and placebo subjects.

SILENOR has not been demonstrated to produce tolerance or physical dependence. In a brief assessment of adverse events observed during discontinuation of doxepin following chronic administration, no symptoms indicative of a withdrawal syndrome were observed.

Abuse potential: Doxepin is not associated with abuse potential in animals or in humans. Healthcare professionals should carefully evaluate patients for history of drug abuse and follow

such patients closely, observing them for signs of misuse or abuse of doxepin (e.g., escalation of dose, drug-seeking behaviours).

Driving and Operating Machinery

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug. This includes potential impairment of the performance of such activities that may occur the day following ingestion of SILENOR.

Hepatic/Biliary/Pancreatic

The effects of hepatic impairment on the pharmacokinetics of SILENOR have not been studied. Because doxepin is extensively metabolized by hepatic enzymes, patients with hepatic impairment may display higher doxepin concentrations than healthy individuals (see 4.2 Recommended Dose and Dosage Adjustment).

Psychiatric

***Depression*:** SILENOR should be administered with caution when prescribed to patients with signs and symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g., intentional overdose) is high in patients with depression and thus, the least amount of drug should be available to them at any given time.

Worsening of depression and suicidal ideation: In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported. As with other hypnotics, SILENOR should be administered with caution in patients with depression. The risk of suicide due to pre-existing psychiatric disorders remains, even when the patient's insomnia improves.

Doxepin, the active ingredient in SILENOR, is an antidepressant at doses 10- to 100-fold higher than SILENOR. Antidepressants increased the risk compared to placebo of suicidal thinking and behaviours (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Risk from the lower dose of doxepin in SILENOR cannot be excluded.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviours listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behaviours sign or symptom of concern requires careful and immediate evaluation.

Renal

The effects of renal impairment on the pharmacokinetics of SILENOR have not been studied. Because only small amounts of doxepin and nordoxepin are eliminated in the urine, renal impairment is not expected to result in significantly altered doxepin concentrations.

Respiratory

Patients with sleep apnea: SILENOR has not been studied in patients with obstructive sleep apnea. Since hypnotics have the capacity to depress respiratory drive, precautions should be

taken if SILENOR is prescribed to patients with compromised respiratory function. In patients with severe sleep apnea, SILENOR is not recommended for use.

7.1 Special PopulationsPregnant Women

There are no adequate and well-controlled studies of SILENOR in pregnant women. SILENOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of doxepin to pregnant animals resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 6 mg/day.

When doxepin (30, 100 and 150 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, developmental toxicity (increased incidences of fetal structural abnormalities and decreased fetal body weights) was noted at ≥ 100 mg/kg/day. The plasma exposures (AUC) at the no-effect dose for embryo-fetal developmental toxicity in rats (30 mg/kg/day) are approximately 6 and 3 times the plasma AUCs for doxepin and nordoxepin (the primary metabolite in humans), respectively, at the MRHD. When administered orally to pregnant rabbits (10, 30 and 60 mg/kg/day) during the period of organogenesis, fetal body weights were reduced at the highest dose in the absence of maternal toxicity. The plasma exposures (AUC) at the no-effect dose for developmental effects (30 mg/kg/day) are approximately 6 and 18 times the plasma AUCs for doxepin and nordoxepin, respectively, at the MRHD. Oral administration of doxepin (10, 30 and 100 mg/kg/day) to rats throughout the pregnancy and lactation periods resulted in decreased pup survival and transient growth delay at the highest dose. The plasma exposures (AUC) at the no-effect dose for adverse effects on pre- and postnatal development in rats (30 mg/kg/day) are approximately 3 and 2 times the plasma AUCs for doxepin and nordoxepin, respectively, at the MRHD.

Labor and/or Delivery: The effects of SILENOR on labor and delivery in pregnant women have not been studied.

7.1.2 Breast-feeding

SILENOR is excreted in human milk after oral administration. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking higher dose of doxepin to treat depression. Therefore, the administration of SILENOR to nursing mothers is not recommended.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of SILENOR in pediatric patients have not been evaluated. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): A total of 362 subjects who were ≥ 65 years and 86 subjects who were ≥ 75 years received SILENOR in controlled clinical studies. No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects but greater

sensitivity of some older individuals cannot be ruled out as sleep-promoting drugs may cause confusion and over-sedation in elderly (see 4.2 Recommended Dose and Dosage Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse reaction overview

The most common reported adverse drug reactions with SILENOR were somnolence, sedation and nausea. There was no apparent overall relationship to dose for any adverse reaction other than for the combined adverse events of somnolence and sedation.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

During the SILENOR clinical development program, a total of 1,017 subjects were exposed to doses of 1 mg to 6 mg of doxepin. The safety of SILENOR has been evaluated in three Phase 3 long-term placebo-controlled clinical trials (ranging from 28 to 85 days) conducted in adults (n = 221) and elderly (n = 494) subjects with chronic insomnia.

The percentage of subjects discontinuing Phase 1, 2, and 3 trials for an adverse reaction was 0.6 % in the placebo group compared to 0.4 %, 1.3 %, and 0.8 % in the SILENOR 1 mg, 3 mg, and 6 mg groups, respectively. No reaction that resulted in discontinuation occurred at a rate greater than 0.5 %.

Table 2 lists the treatment-emergent adverse events, regardless of causality, reported by at least 1% of subjects who received SILENOR (3 mg or 6 mg) in the three long-term chronic insomnia studies (n = 221 for adult; and n = 417 for elderly).

Table 2 – Treatment-Emergent Adverse Events Reported at a Frequency ≥ 1 % of Subjects in Long-Term Chronic Insomnia Studies

System Organ Class Preferred term n (%)	SILENOR 3 mg (n = 157)	SILENOR 6 mg (n = 203)	Placebo (n = 278)
Blood and lymphatic system disorders			
Anemia	0	2 (1.0)	0
Gastrointestinal disorders			
Nausea	3 (1.9)	5 (2.5)	3 (1.1)
Dry mouth	2 (1.3)	3 (1.5)	3 (1.1)
Vomiting	0	3 (1.5)	2 (0.7)
Stomach discomfort	2 (1.3)	0	0
General disorders and administration site conditions			
Chest pain	2 (1.3)	1 (0.5)	0
Infections and infestations			

System Organ Class Preferred term n (%)	SILENOR 3 mg (n = 157)	SILENOR 6 mg (n = 203)	Placebo (n = 278)
Upper respiratory tract infection	3 (1.9)	3 (1.5)	3 (1.1)
Nasopharyngitis	3 (1.9)	1 (0.5)	2 (0.7)
Gastroenteritis	3 (1.9)	0	0
Tooth infection	2 (1.3)	0	1 (0.4)
Injury, poisoning and procedural complications			
Post procedural complication	2 (1.3)	1 (0.5)	0
Fall	2 (1.3)	0	2 (0.7)
Joint sprain	2(1.3)	0	1 (0.4)
Investigations			
Blood glucose increased	2 (1.3)	0	0
Metabolism and nutrition disorders			
Anorexia	2 (1.3)	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.6)	2 (1.0)	1 (0.4)
Back pain	2 (1.3)	1 (0.5)	1 (0.4)
Nervous system disorders			
Somnolence	9 (5.7)	11 (5.4)	12 (4.3)
Sedation	1 (0.6)	7 (3.4)	0
Somnolence and Sedation Combined	10 (6.4)	18 (8.9)	12 (4.3)
Dizziness	2 (1.3)	3 (1.5)	3 (1.1)
Paresthesia	0	2 (1.0)	2 (0.7)
Dysgeusia	0	2 (1.0)	0
Psychiatric disorders			
Abnormal dreams	2 (1.3)	0	0
Anxiety	0	2 (1.0)	0
Vascular disorders			
Hypertension	4 (2.5)	1 (0.5)	0

Table 3 lists the treatment-emergent adverse events, regardless of causality, by age group reported by at least 2 % of subjects who received SILENOR in the three long-term chronic insomnia studies.

Table 3 – Treatment-Emergent Adverse Events Reported at a Frequency ≥ 2 % of Adults or Elderly Subjects in the Three Long-Term Chronic Insomnia Studies

Preferred Term n (%)	Adult Subjects		Elderly Subjects	
	All SILENOR* (n = 148)	Placebo (n = 73)	All SILENOR* (n = 212)	Placebo (n = 205)
Somnolence	11 (7.4 %)	4 (5.5 %)	9 (4.2 %)	8 (3.9 %)
Nausea	7 (4.7 %)	0	1 (0.5 %)	3 (1.5 %)
Sedation	2 (1.4 %)	0	6 (2.8 %)	0
Dizziness	0	1 (1.4 %)	5 (2.4 %)	2 (1.0 %)
Dry Mouth	0	0	5 (2.4 %)	3 (1.5 %)
Upper Respiratory Tract Infection	3 (2.0 %)	1 (1.4 %)	3 (1.4 %)	2 (1.0 %)
Post Procedural Complication	3 (2.0 %)	0	0	0

*includes SILENOR doses ranging from 3 mg to 6 mg.

Treatment-emergent adverse events generally occurred with similar incidence in adults and elderly subjects with the exception with nausea (4.7 % in adults versus 0.5 % in elderly).

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events were reported in the administration of SILENOR at a frequency < 1 % in the three long-term chronic insomnia safety and efficacy studies.

Cardiac disorders: atrioventricular block, tachycardia

Ear and labyrinth disorders: hypoacusis, motion sickness, tinnitus

Eye disorders: blepharospasm, diplopia, eye pain, vision blurred, visual disturbance

Gastrointestinal disorders: abdominal pain upper, diarrhoea, gastroesophageal reflux disease, gingival recession, toothache, tooth fracture

General disorders: fatigue, feeling abnormal, hangover, oedema peripheral, pitting oedema, sluggishness

Infections and infestations: bronchitis, eye infection, fungal infection, gastroenteritis viral, herpes zoster, infective tenosynovitis, influenza, laryngitis, lower respiratory tract infection, onychomycosis, sinusitis, tooth abscess, urinary tract infection, viral infection

Injury, poisoning and procedural complications: back injury, excoriation, foot fracture, hand fracture, skin laceration, upper limb fracture

Investigations: blood pressure decreased, electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, hypokalemia, increased appetite

Musculoskeletal and connective tissue disorders: joint range of motion decreased, muscle cramp, myalgia, neck pain, pain in extremity

Neoplasm benign, malignant and unspecified (including cysts and polyps): lung adenocarcinoma stage I, malignant melanoma

Nervous system disorders: ageusia, ataxia, disturbance in attention, lethargy, migraine, sleep paralysis, tremor

Psychiatric disorders: depression, elevated mood, libido decreased, nightmare

Renal and urinary disorders: enuresis

Reproductive system and breast disorders: breast cyst

Respiratory, thoracic and mediastinal disorders: cough, nasal congestion, nasopharyngeal disorder, pharyngolaryngeal pain, sinus congestion

Skin and subcutaneous tissue disorders: dermatitis contact, erythema, pruritus generalized, rash, rosacea, skin lesion

Vascular disorders: blood pressure inadequately controlled, hematoma

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

There were no clinically relevant findings in the mean values and mean changes in clinical laboratory data after any of the treatments.

8.5 Post-Market Adverse Reactions

The following adverse events have been reported in users of SILENOR in the post marketing period. These adverse events are compiled from spontaneous reports and are listed regardless of frequency and whether or not a causal relationship with SILENOR has been established. Adverse events previously observed in clinical trials are not duplicated below.

Cardiac disorders: palpitations

Eye disorders: dry eye, lacrimation decreased, ocular hyperemia, visual acuity reduced

Gastrointestinal disorders: abdominal discomfort, bowel movement irregularity, dyspepsia, flatulence

General disorders: energy increased, epistaxis, feeling drunk, hypotrichosis, irritability, stress symptoms

Injury, poisoning and procedural complications: intentional overdose

Investigations: dysuria, hyperglycemia, hypoglycemia, swollen tongue, urine output decreased, urine output increased, weight increased

Musculoskeletal and connective tissue disorders: muscle spasms

Nervous system disorders: drowsiness, dyskinesia, head discomfort, nervousness, poor quality sleep, psychomotor hyperactive, restless leg syndrome, restlessness

Psychiatric disorders: amnesia, hallucination, insomnia, mental impairment, mood altered, sleep disorder, suicidal ideation, suicidal thoughts, thinking abnormal

Renal and urinary disorders: micturition urgency, urinary hesitation

Respiratory, thoracic and mediastinal disorders: dyspnea, hoarseness, pharyngeal hypoesthesia, pharyngeal edema, throat irritation

Skin and subcutaneous tissue disorders: hyperhidrosis, night sweats, rash generalized

Vascular disorders: hot flush

9 DRUG INTERACTIONS

9.1 Serious drug interactions

- Co-administration with monoamine oxidase inhibitors (MAOIs) (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

SILENOR is primarily metabolized by hepatic cytochrome P450 isozymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C9. Inhibitors of these isozymes may increase the exposure of doxepin. SILENOR is not an inhibitor of any CYP isozymes at therapeutically relevant concentrations. The ability of SILENOR to induce CYP isozymes is not known.

Since doxepin is metabolized by CYP2C19 and CYP2D6, inhibitors of these CYP isozymes may increase the exposure of doxepin.

9.3 Drug-Behavioural Interactions

SILENOR may potentiate the sedative effects of alcohol. Patients should not consume alcohol with SILENOR.

9.4 Drug-Drug Interactions

SILENOR may potentiate the sedative effects of sedating antihistamines and other CNS depressants.

Table 4 – Established or Potential Drug-Drug Interactions

Proper/common name	Source of Evidence	Effect	Clinical comment
CNS Depressants (e.g., barbiturates), and Sedating Antihistamines	T	Potential additive effects of SILENOR used in combination with CNS depressants or sedating antihistamines.	Patients should be cautioned about this effect.
Cimetidine	CT	When cimetidine 300 mg BID was co-administrated with a single dose of SILENOR 6 mg, there was approximately a 2-fold increase in SILENOR C_{max} and AUC compared to SILENOR given alone.	A maximum dose of 3 mg is recommended in adults and elderly when cimetidine is co-administered with SILENOR.
Sertraline	CT	Following co-administration of doxepin 6 mg with sertraline 50 mg (at steady-state), a modest pharmacokinetic drug interaction was observed; the doxepin mean $AUC_{0-\infty}$ and C_{max}	–

Proper/common name	Source of Evidence	Effect	Clinical comment
		estimates were approximately 21% and 32% higher, respectively, than those obtained following administration of doxepin alone.	
Inhibitors or substrates of CYP2D6 (e.g., quinidine, selective serotonin reuptake inhibitors [SSRIs])	T	May increase the plasma concentration of TCAs when administered concomitantly.	–
Phenytoin	T	Potential phenytoin toxicity when administered concomitantly, as phenytoin and SILENOR use the same CYP2C19 metabolism pathway	
Sympathomimetic agents (e.g., ephedrine, phenylephrine and phenylpropanolamine)	T	Potential exaggerated symptoms of hypertension and tachycardia.	The literature reports these potential symptoms as likely dose related and may not be appear with doses lower than 25 mg/day. Hence, close supervision and careful adjustment of dosages is required when doxepin is administered with sympathomimetic agents.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

SILENOR is readily absorbed from the gastrointestinal tract. When administered with a high-fat meal, the AUC for a single 6 mg dose was increased by 41 % and the C_{max} was 15 % higher than when given in a fasted state. Additionally, compared to the fasted state, the time to reach maximum plasma concentration (T_{max}) was delayed by approximately 3 hours. Therefore, for faster onset and to minimize the potential for next day effects, it is recommended not to take SILENOR within 3 hours of a meal (see 4.1 Dosing Considerations and 10.3 Pharmacokinetics).

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 exact mechanism by which doxepin exerts its sleep maintenance effect is unknown but it is well established that doxepin is one of the most potent H_1 antagonist and has a substantial selectivity for H_1 receptors (Ki < 1 nM) versus other CNS and peripheral targets. Doxepin has an affinity toward the human 5-HT_{2a} receptor; this property could play a role in promoting sleep maintenance, as several studies have proposed that antagonism at this site promotes restorative Stage III-IV sleep.

10.2 Pharmacodynamics

Cardiovascular

Cardiac safety: In a thorough QTc prolongation study in healthy subjects, doxepin had no effect on QT intervals or other electrocardiographic parameters after multiple daily doses of 6 mg or 50 mg.

***In vitro* studies:** The effect of doxepin on IKr channels (encoded by hERG; human Ether-à-go-go Related Gene) has been investigated. Doxepin was found to inhibit IHERG channels with an IC_{50} of 6.5 ± 1.4 mcM and native IKr with an IC_{50} of 4.4 ± 0.6 mcM. This concentration is approximately 1300-fold higher than the concentration reached with the highest strength of SILENOR (6 mg tablets, approximately 3.4 nM C_{max}=1.094 ng/mL).

***In vivo* studies:** Doxepin elicits either positive or negative inotropic effects depending on species, decreases in blood pressure, and dysrhythmias characterized by broadening of the QRS complex and QT prolongation. In studies where plasma concentrations are reported, these events typically occur at concentrations well in excess of 1000 ng/mL, or more than 1000 times the maximum mean concentrations (at 6 mg).

Clinical electrocardiography studies: In a double-blind, randomized, placebo-controlled, parallel group study in healthy subjects (n = 44-50/treatment arm), serial ECG recordings were collected on day 7 of treatment with doxepin at a therapeutic dose of 6 mg and a supratherapeutic dose of 50 mg. Doxepin 6 mg and doxepin 50 mg did not affect the QTc interval, the QRS duration, or the PR interval. Heart rate was not affected at the 6 mg dose, but statistically significant increases in heart rate were observed at the 50 mg dose, with a maximum placebo-adjusted mean change from baseline of 6.5 bpm (90% CI 4.3, 8.6).

Doxepin was associated with a blood pressure-lowering effect. Serial blood pressure measurements were performed on day 1 of treatment at predose and at 2, 4, 8, 12, and 24 h post-dosing. Doxepin 6 mg was associated with a statistically significant placebo-adjusted decrease from baseline in systolic blood pressure at 4 h post-dosing: mean -2.92 mmHg (90 % CI -5.39, -0.45). Statistically significant reductions in diastolic blood pressure were reported at 4, 8, and 12 h post-dosing with doxepin 6 mg, with a maximum decrease at 8 h post-dosing: mean -4.67 mmHg (90 % CI -6.78, -2.55).

Doxepin 50 mg was associated with statistically significant placebo-adjusted decreases from baseline in systolic blood pressure at all post-dose time points on day 1. The largest observed decrease in systolic blood pressure occurred at 8 h post-dose: mean -7.09 mmHg (90 % CI -9.56, -4.62). Diastolic blood pressure was significantly reduced at 2, 4, 8, and 12 h post-dosing in the doxepin 50 mg group. The maximum observed decrease in diastolic blood pressure occurred at 8 h post-dosing: mean -6.68 mmHg (90 % CI -8.80, -4.57).

The C_{max} and AUC values of doxepin following treatment with the 50 mg dose for 7 days were 12-fold higher than for the 6 mg dose.

Studies Pertinent to Safety Concerns for Sleep-promoting Drugs

Residual Pharmacological Effect in Insomnia Trials: Five randomized placebo-controlled studies in adults and the elderly assessed next-day psychomotor function within 1 hour of awakening utilizing the digit-symbol substitution test (DSST), symbol copying test (SCT), and visual analog scale (VAS) for sleepiness, following night time administration of SILENOR.

In a one-night, double-blind study conducted in 565 healthy adult subjects experiencing transient insomnia, SILENOR 6 mg showed modest negative changes in SCT and VAS.

In a 35-day, double-blind, placebo-controlled, parallel group study of SILENOR 3 and 6 mg in 221 adults with chronic insomnia, small decreases in the DSST and SCT occurred in the 6 mg group.

In a 3-month, double-blind, placebo-controlled, parallel group study in 240 elderly subjects with chronic insomnia, SILENOR 1 mg and 3 mg was comparable to placebo on DSST, SCT, and VAS.

10.3 Pharmacokinetics

The pharmacokinetics of SILENOR 3 mg and 6 mg have been characterized in healthy subjects.

Table 5 – Summary of Doxepin Pharmacokinetic Parameters in Healthy Volunteers Following a Single Dose of 6 mg

	C_{max} (ng/mL)	**T_{max}** (h)	**$t_{½}$** (h)	**$AUC_{0-\infty}$** (ng*h/mL)
Single dose mean n = 16	0.8864 (59.4)	3.5 (2.0 – 6.0)	15.32 (31.3)	15.19 (69.1)

Estimates presented are arithmetic mean (CV %) for AUC, C_{max}, and $t_{1/2}$ and median (range) for T_{max}.

Absorption: After oral administration of a 6 mg dose to fasted healthy subjects, doxepin plasma concentrations increase rapidly, with peak concentrations (median T_{max}) occurring 3.5 hours postdose. Peak plasma concentrations (C_{max}) and total exposure (AUC) of SILENOR increased in a dose-proportional manner for 3 mg and 6 mg doses.

SILENOR is readily absorbed from the gastrointestinal tract. When administered with a high-fat meal, the AUC for a single 6 mg dose was increased by 41 % and the C_{max} was 15 % higher than when given in a fasted state. Additionally, compared to the fasted state, the time to reach maximum plasma concentration (T_{max}) was delayed by approximately 3 hours. Therefore, for faster onset and to minimize the potential for next day effects, it is recommended not to take SILENOR within 3 hours of a meal.

Distribution: SILENOR is highly lipophilic and widely distributed throughout the body tissues. The mean apparent volume of distribution following a single 6 mg oral dose of SILENOR in healthy subjects was 11,930 liters. SILENOR is approximately 80% bound to plasma proteins.

Metabolism: Following oral administration, SILENOR is extensively metabolized by oxidation and demethylation. The primary metabolite is *N*-desmethyldoxepin (nordoxepin). The primary metabolites undergo further biotransformation to glucuronide conjugates. *In vitro* studies have shown that CYP2C19 and CYP2D6 are the major enzymes involved in doxepin metabolism, and that CYP1A2 and CYP2C9 are involved to a lesser extent.

In animals, data shows that doxepin is well absorbed, widely distributed, moderately protein bounded, and undergoes extensive Phase I and Phase II metabolism, the most important pathways being demethylation, hydroxylation and glucuronidation. Doxepin metabolism appears to be similar for humans and animal species and is isomer specific, with demethylation reactions occurring for both isomers primarily via CYP2C19 (with contribution of 1A2, 2C9 and possibly 3A4), while only the E isomer is hydroxylated via CYP2D6. Doxepin, as well as oxidative metabolites and conjugates of doxepin and its isomers are rapidly eliminated and the majority of drug products are recovered in urine.

Excretion: Doxepin is excreted in the urine mainly in the form of glucuronide conjugates. Less than 3% of a doxepin dose is excreted in the urine as parent compound or nordoxepin. The apparent terminal half-life ($t_{1/2}$) of doxepin is 15.3 hours and 31 hours for nordoxepin.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of SILENOR have not been studied in subjects under 18 years of age.
- **Geriatrics:** The pharmacokinetics of SILENOR have not been studied in elderly subjects. Elimination of doxepin may be slower and the terminal half-life may be longer in the elderly, which may result in drug accumulation and a greater risk of undesirable effects.
- **Gender:** No gender effect was observed in healthy subject/patients after repeated administration of SILENOR.
- **Hepatic Insufficiency:** No studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of SILENOR. Because doxepin is extensively metabolized by hepatic enzymes, patients with hepatic insufficiency may display higher doxepin concentrations than healthy individuals.
- **Renal Insufficiency:** No studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of SILENOR. Because only small amounts of doxepin and nordoxepin are eliminated in the urine, renal impairment would not be expected to result in significantly altered doxepin concentrations.
- **Genetic Polymorphism:** Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.
- **Drug Interactions**: Since doxepin is metabolized by CYP2C19 and CYP2D6, inhibitors of theses CYP isozymes may increase the exposure of doxepin.

11 STORAGE, STABILITY AND DISPOSAL

Keep SILENOR out of reach and sight of children. Store SILENOR at room temperature between 15°C and 30°C. Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

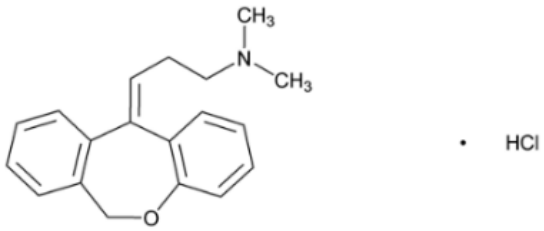
Drug Substance

Proper name: doxepin hydrochloride

Chemical name: Isomeric mixture of 1-propanamine, 3-dibenz[*b,e*]oxepin-11(6*H*)ylidene- *N,N*-dimethyl-hydrochloride

Molecular formula and molecular mass: $C_{19}H_{21}NO \cdot HCl$ and 315.84 g/mol

Structural formula:



Physicochemical properties: Doxepin hydrochloride is a white crystalline powder, with a slight amine-like odor, that is readily soluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Insomnia

The efficacy of SILENOR for improving sleep maintenance was supported by six randomized, double-blind studies up to 3 months in duration that included 1,423 subjects, 18 to 93 years of age, with chronic (n = 858) or experimentally induced transient (n = 565) insomnia. SILENOR was evaluated at doses of 1 mg, 3 mg, and 6 mg relative to placebo in inpatient (sleep laboratory) and outpatient settings.

The primary efficacy measures for assessment of sleep maintenance were the objective and subjective time spent awake after sleep onset (respectively, objective Wake After Sleep Onset [WASO] and subjective WASO).

Subjects in studies of chronic insomnia were required to have at least a 3-month history of insomnia.

Rebound Insomnia Effects

Rebound insomnia, defined as a worsening in WASO compared with baseline following discontinuation of treatment, was assessed in a double-blind, 35-day study (followed by 2 days of drug discontinuation – i.e.: Day 36 and 37) in adults with chronic insomnia. SILENOR 3 mg and 6 mg showed little evidence of rebound insomnia in the two nights following discontinuation. However, there was evidence of mild discontinuation effects on latency to persistent sleep (LPS)

in the two nights following SILENOR discontinuation.

Study Results

Chronic Insomnia

Adults: A randomized, double-blind, parallel-group study was conducted in adults (n = 221) with chronic insomnia. SILENOR 3 mg and 6 mg was compared to placebo out to 30 days. SILENOR 3 mg and 6 mg were superior to placebo on objective WASO and TST (total sleep time). SILENOR 3 mg was superior to placebo on subjective WASO at night 1 only. SILENOR 6 mg was superior to placebo on subjective WASO at night 1, and nominally superior at some later time points out to Day 30. SILENOR 3 mg was superior to placebo on subjective TST at night 1 only. SILENOR 6 mg was superior to placebo on subjective TST at night 1, and at some later time points. On other secondary subjective outcome measures a similar pattern was observed, suggesting superior efficacy of the SILENOR 6 mg dose compared to the 3 mg dose.

Elderly: Elderly subjects with chronic insomnia were assessed in two parallel-group studies.

The first randomized, double-blind study assessed SILENOR 1 mg and 3 mg relative to placebo for 3 months in inpatient and outpatient settings in elderly subjects (n = 240) with chronic insomnia. SILENOR 3 mg, but not 1 mg, was superior to placebo on objective and subjective WASO. The second randomized, double-blind study assessed SILENOR 6 mg relative to placebo for 4 weeks in an outpatient setting in elderly subjects (n = 254) with chronic insomnia. On subjective WASO, SILENOR 6 mg was superior to placebo.

Transient Insomnia

Healthy adult subjects (n = 565) experiencing transient insomnia (induced by a 3 hour phase advance) during the first night in a sleep laboratory were evaluated in a randomized, double-blind, parallel-group, single-dose study of SILENOR 6 mg relative to placebo. SILENOR 6 mg was superior to placebo on objective WASO and subjective WASO.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Repeat Dose Toxicity: In multiple-dose studies in rats, clinical signs of CNS depression were observed, with the addition of decreases in body weight and food consumption. However, there was no consistent evidence of target organ toxicity. Doxepin-related decreased body weight and body weight gain was also noted in animals receiving 100 mg/kg/day. Alkaline phosphatase was increased in males at 100 mg/kg/day. There were no doxepin-related macroscopic findings in either sex. There were no effects on hematology, coagulation, or urinalysis parameters. Possible doxepin-related organ weight changes were present in the liver, spleen, and thymus. Increases in liver weight were present in males and females at 25, 50, and 100 mg/kg/day. Decreased spleen weights were observed in males and females at 100 mg/kg/day and in females only at 25

and 50 mg/kg/day. No correlative microscopic findings were present in the livers or spleens. Thymus weight was decreased in both sexes at 100 mg/kg/day. These decreases in thymus weights corresponded with minimal to mild lymphoid depletion microscopically.

Carcinogenicity: No evidence of carcinogenic potential was observed when doxepin was administered orally to hemizygous Tg.rasH2 mice for 26 weeks at doses of 25, 50, 75 and 100 mg/kg/day. Doxepin has shown no oncogenic effect when administered daily to rats for 104 weeks at doses of 10, 30 and 75 mg.

Genotoxicity: Doxepin was negative in *in vitro* (bacterial reverse mutation, chromosomal aberration in human lymphocytes) and *in vivo* (rat micronucleus) assays.

Reproductive and Developmental Toxicology: When doxepin (10, 30 and 100 mg/kg/day) was orally administered to male and female rats prior to, during and after mating, adverse effects on fertility (increased copulatory interval and decreased corpora lutea, implantation, viable embryos and litter size) and sperm parameters (increased percentages of abnormal sperm and decreased sperm motility) were observed. The plasma exposures (AUC) for doxepin and nordoxepin at the no-effect dose for adverse effects on reproductive performance and fertility in rats (10 mg/kg/day) are less than those in humans at the maximum recommended human dose of 6 mg/day (approx. 53 to 61-fold).

Patient Medication Information

READ THIS FOR THE SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSILENOR®

doxepin tablets

This Patient Medication Information is written for the person who will be taking **SILENOR**. 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 **SILENOR**, talk to a healthcare professional.

What SILENOR is used for:

SILENOR is used to treat adults who have trouble staying asleep.

How SILENOR works:

SILENOR belongs to a group of medicines known as tricyclic antidepressants. It is not known exactly how SILENOR works, but it is thought to reduce the release of a chemical called histamine in your body. Reducing this chemical helps to promote and maintain sleep.

The ingredients in SILENOR are:

Medicinal ingredient: doxepin hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, D&C yellow no. 10 aluminum lake (6 mg tablets only), FD&C blue no. 1 aluminum lake, magnesium stearate and microcrystalline cellulose

SILENOR comes in the following dosage forms:

Tablets: 3 mg and 6 mg

Do not use SILENOR if:

- you are allergic to doxepin hydrochloride, other dibenzoxepine compounds, or to any of the other ingredients in SILENOR (see **The ingredients in SILENOR are:**)
- you have an eye problem called narrow angle glaucoma that is not being treated
- you have difficulty urinating
- you take a monoamine oxidase inhibitor (MAOI) medicine or have taken an MAOI in the last 14 days (2 weeks). Ask your healthcare professional if you are not sure if your medicine is an MAOI.

Talk to your healthcare professional before taking this medicine if you have any of these conditions.

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

- suffer from depression or have a history of depression and/or suicidal thoughts
- have breathing problems at night (sleep apnea)
- have a liver disease
- have a history of drug or alcohol abuse or addiction
- are pregnant, plan to become pregnant or you become pregnant while taking this medication
- are breastfeeding or plan to breastfeed. SILENOR may pass into your milk and may harm your baby. You should not breastfeed while taking SILENOR.

Other warnings you should know about:

Sleep problems can be a symptom of many physical and/or psychiatric disorders. Your healthcare professional will evaluate your medical history before starting treatment with SILENOR. **If your sleep problems get worse or do not get better within 7 to 10 days, talk to your healthcare professional.** This may mean that there is another condition causing your sleep problem.

Complex Sleep Behaviours: SILENOR can cause dangerous sleeping-related behaviours such as getting out of bed while not fully awake and doing activities that you do not know you are doing. You may not remember doing these activities when you wake up. These unusual behaviours may occur whether or not you drink alcohol but is more likely to occur with alcohol. These behaviours may also occur if you take other medicines that can make you sleepy, such as medicines used to treat depression or anxiety. The activities you may do in these situations can put you and people around you in danger. This can include driving a car ("sleep-driving"), leaving the house, making and eating food, having sex and talking on the phone. These behaviours can cause serious injuries, including death.

You and people close to you should watch out for unusual types of behaviour when you are asleep. If you find out that you have done any such activities for which you have no memory, you should stop taking SILENOR and call your healthcare professional right away.

Depression or Suicide: If you have thoughts of harming or killing yourself at any time, talk to a healthcare professional or go to a hospital **right away**. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses. Ask them to read this leaflet. You might ask them to tell you if they:

- think your depression or mental illness is getting worse, or
- are worried about changes in your behaviour.

Driving and Using Machines: SILENOR can affect your ability to drive and operate machinery. Do not drive or operate machinery until you know how SILENOR affects you.

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

Serious drug interactions

- Do NOT take SILENOR if you take a monoamine oxidase inhibitor (MAOI) medicine or have taken an MAOI in the last 14 days (2 weeks). Ask your healthcare professional if you are not sure if your medicine is an MAOI.

The following may also interact with SILENOR:

- alcohol. **Do not use SILENOR** if you drink alcohol.
- other hypnotics or sedatives that are used to help with sleeping
- certain allergy medicines (antihistamines)
- other medicines that can make you sleepy or affect your breathing (narcotic analgesics)
- medicines used to control or prevent convulsions (anticonvulsants)
- mood altering drugs, which themselves can make you sleepy (antipsychotics, antidepressants and other psychotropic medications)
- cimetidine (an anti-acid medication)
- medicines that block, or are a substrate of an enzyme called "CYP2D6", such as quinidine and selective serotonin reuptake inhibitors (SSRIs)
- medicines that mimic the effects of the sympathetic nervous system (sympathomimetics), such as ephedrine, phenylephrine and phenylpropanolamine

How to take SILENOR:

- Take SILENOR exactly as your healthcare professional tells you to take it.
- **Take SILENOR within 30 minutes of bedtime.** After taking SILENOR, you should only do activities to get ready for bed.
- Only take SILENOR if you are able to get a full night of sleep (7 to 8 hours).
- To minimize any next day side effects, do NOT take SILENOR within 3 hours of a meal.
- **Remember:** This medication is for you only. Never give it to others. It may harm them even if their symptoms are the same as yours.

Usual dose:

Adults: The recommended dose is 6 mg once daily. Depending on your response, your healthcare professional may decrease your daily dose to 3 mg.

Elderly (65 years of age and older): The recommended starting dose is 3 mg once daily. Depending on your response, your healthcare professional may increase your daily dose to 6 mg.

The maximum daily dose is 6 mg.

Overdose:

If you think you, or a person you are caring for, have taken too much SILENOR, 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 your dose at bedtime, wait and take your next dose at your regular time the next night. Do NOT take 2 doses at the same time to make up for a missed dose.

Possible side effects from using SILENOR:

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

Side effects may include:

- sleepiness or drowsiness
- nausea or vomiting
- headache
- dry mouth
- stomach pain
- upper respiratory tract infection
- a cold
- diarrhea
- tooth infection
- falls or joint sprains
- joint stiffness or back pain
- tingling or prickling
- altered sense of taste
- abnormal dreams
- anxiety

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Somnambulism (sleepwalking): getting out of bed while not fully awake and doing activities you do not remember the day after			✓
VERY RARE			
Thoughts of death or suicide			✓

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

Storage:

Store at room temperature between 15°C and 30°C and protect from light.

Keep out of reach and sight of children.

If you want more information about SILENOR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://knighttx.com), by emailing medinfo@knighttx.com, or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

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