PRODUCT MONOGRAPH

Pr SILENOR®

Doxepin tablets

3 and 6 mg doxepin as doxepin hydrochloride

Hypnotic

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SILENOR®

doxepin hydrochloride tablets

3 mg and 6 mg doxepin as doxepin hydrochloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet of 3 and 6 mg doxepin	Colloidal silicon dioxide, microcrystalline cellulose and magnesium stearate

INDICATIONS AND CLINICAL USE

Sleeping disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should be made after the patient has been carefully evaluated.

SILENOR (doxepin hydrochloride) 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).

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.

Pediatrics (< 18 years of age):

The safety and effectiveness of SILENOR in pediatric patients have not been evaluated.

CONTRAINDICATIONS

SILENOR is contraindicated in patients with known intolerance or hypersensitivity to doxepin HCl, other dibenizoxepines compounds or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

SILENOR is contraindicated in individuals with untreated narrow angle glaucoma or severe urinary retention.

Serious side effects and even death have been reported following the concomitant use of certain drugs with monoamine oxidase inhibitors (MAOIs). SILENOR is therefore contraindicated in patients currently taking MAOIs or in patients who have used MAOIs within the past two weeks.

WARNINGS AND PRECAUTIONS

General

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient.

The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness or the presence of sleep state misperception. Worsening of insomnia or the emergence of new abnormalities of thinking or behaviour may be the consequence of an unrecognized psychiatric or physical disorder.

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 behaviour episode.

Central Nervous System Depressant Effects

When taken with SILENOR, the sedative effects of other Central Nervous System (CNS) depressants, sedating antihistamines and alcoholic beverages may be potentiated (see **DRUG INTERACTIONS**). Patients should not consume alcohol with SILENOR (see **DRUG INTERACTIONS**). Patients should be cautioned about potential additive effects of SILENOR used in combination with CNS depressants or sedating antihistamines.

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.

Drug Abuse and Dependence

Dependence/Tolerance or Withdrawal

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.

Potential for Abuse

Doxepin is not associated with abuse potential in animals or in humans. Physicians 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., esclalation of dose, drug-seeking behaviour).

Hepatic

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 **DOSAGE AND ADMINISTRATION**).

Psychiatric

Depression:

SILENOR should be administrated with caution when prescribed to patients with signs and symptoms of depression that 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 one time.

Suicide risk and worsening of depression:

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of hypnotics.

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 behaviour (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 behaviour sign or symptom of concern requires careful and immediate evaluation.

Renal

The effects of renal impairment on the pharmacokinetics of SILENOR (doxepin) have not been studied. Because only small amounts of doxepin and nordoxepin are eliminated in the urine, renal impairment would not be expected to result in significant 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.

Special Populations

Pregnant 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 Delivery:

The effects of SILENOR on labor and delivery in pregnant women have not been studied.

Nursing Women:

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.

Pediatrics (< 18 years of age):

The safety and effectiveness of SILENOR in pediatric patients have not been evaluated.

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 **DOSAGE AND ADMINISTRATION**).

Patient Counselling Information

A patient information sheet should be provided when SILENOR tablets are dispensed to the patient.

Patients receiving SILENOR should be given the following instructions by the physician:

1. Sleep-driving and Other Complex Behaviors

There have been reports of people getting out of bed after taking a hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when a hypnotic is taken with alcohol or other central nervous system depressants (see Warnings and Precautions and Drug Interactions). Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a hypnotic. As with "sleep-driving", patients usually do not remember these events.

In addition, patients should be advised to report all concomitant medications to the prescriber. Patients should be instructed to report events such as "sleep-driving" and other complex behaviors immediately to the prescriber.

2. Suicide risk and Worsening of Depression:

Patients, their families, and their caregivers should be encouraged to be alert to worsening of depression, including suicidal thoughts and actions. Such symptoms should be reported to the patient's prescriber or health professional.

3. Administration Instructions

Patients should be counseled to take SILENOR within 30 minutes of bedtime and should confine their activities to those necessary to prepare for bed. SILENOR tablets should not be taken within 3 hours of a meal. Advise patients NOT to take SILENOR when drinking alcohol.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 SLENOR 1 mg, 3 mg, and 6 mg groups, respectively. No reaction that resulted in discontinuation occurred at a rate greater than 0.5%.

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

Table 1 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 1: Treatment-emergent adverse events reported at a frequency ≥ 1% of subjects in long-term chronic insomnia studies

System Organ Class **Preferred term**	**Doxepin Dose**		
	Placebo (N=278) n (%)	**Doxepin 3 mg (N=157) n (%)**	**Doxepin 6 mg (N=203) n (%)**
Blood and lymphatic system disorders			
Anaemia	0	0	2 (1.0)
Gastrointestinal disorders			
Nausea	3 (1.1)	3 (1.9)	5 (2.5)
Dry mouth	3 (1.1)	2 (1.3)	3 (1.5)
Vomiting	2 (0.7)	0	3 (1.5)
Stomach discomfort	0	2 (1.3)	0
General disorders and administration site conditions			
Chest pain	0	2 (1.3)	1 (0.5)
Infections and infestations			
Upper respiratory tract infection	3 (1.1)	3 (1.9)	3 (1.5)
Nasopharyngitis	2 (0.7)	3 (1.9)	1 (0.5)
Gastroenteritis	0	3 (1.9)	0
Tooth infection	1 (0.4)	2 (1.3)	0
Injury, poisoning and procedural complications			
Post procedural complication	0	2 (1.3)	1 (0.5)
Fall	2 (0.7)	2 (1.3)	0
Joint sprain	1 (0.4)	2(1.3)	0
Investigations			
Blood glucose increased	0	2 (1.3)	0
Metabolism and nutrition disorders			
Anorexia	0	2 (1.3)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.4)	1 (0.6)	2 (1.0)
Back pain	1 (0.4)	2 (1.3)	1 (0.5)
Nervous system disorders			
Somnolence	12 (4.3)	9 (5.7)	11 (5.4)

Sedation	0	1 (0.6)	7 (3.4)
Somnolence and Sedation Combined	12 (4.3)	10 (6.4)	18 (8.9)
Dizziness	3 (1.1)	2 (1.3)	3 (1.5)
Paraesthesia	2 (0.7)	0	2 (1.0)
Dysgeusia	0	0	2 (1.0)
Psychiatric disorders			
Abnormal dreams	0	2 (1.3)	0
Anxiety	0	0	2 (1.0)
Vascular disorders			
Hypertension	0	4 (2.5)	1 (0.5)

Table 2 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 2: Treatment-emergent adverse events reported at a frequency ≥ 2% of adults or elderly subjects in the three long-term chronic insomnia studies

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

* includes doxepin 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).

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.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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: 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, gastrooesophageal 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, hypokalaemia, 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 (incl 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 generalised, rash, rosacea, skin lesion.

Vascular disorders: blood pressure inadequately controlled, haematoma.

Abnormal Hematologic and Clinical Chemistry Findings

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

Post-Market Adverse Drug 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 hyperaemia, 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, hypoglycaemia, 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: dyspnoea, hoarseness, pharyngeal hypoaesthesia, pharyngeal oedema, throat irritation.

Skin and subcutaneous tissue disorders: hyperhydrosis, night sweats, rash generalized.

Vascular disorders: hot flush.

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.

Drug-Drug Interactions

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

Established or Potential Drug-Drug Interactions

Class of Compound	Reference	Effect	Clinical comment
CNS Depressants, and Sedating Antihistamines	Theoretical	Potential additive effects of SILENOR used in combination with CNS depressants or sedating antihistamines.	Patients should be cautioned about this effect.
Alcohol	Theoretical	SILENOR may potentiate the sedative effects of alcohol.	Patients should not consume alcohol with SILENOR.
Cimetidine	Clinical Trial	When cimetidine 300 mg BID was co-administrated with a single dose of SILENOR 6mg, there was approximately a 2-fold increase in SILENOR Cmax 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 (see **ACTION AND CLINICAL PHARMACOLOGY**).
Sertraline	Clinical Trial	Following co-administration of doxepin 6 mg with sertraline 50 mg (at steady-state), a modest pharmacokinetic drug interaction was observed; the doxepin mean AUC0-∞ and Cmax estimates were approximately 21% and 32% higher, respectively, than those obtained following administration of doxepin alone.	

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 Dosage and **ADMINISTRATION ACTION** and **CLINICAL PHARMACOLOGY**).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyle products have not been established.

DOSAGE AND ADMINISTRATION

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 **ACTION AND CLINICAL PHARMACOLOGY**).

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.

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

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

Use in Children (< 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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 SINEQUAN (doxepin HCl) is more likely to be manifested by increased psychomotor agitation and convulsions leading to apnea and coma. The ECG changes (broadening of QRS and T- wave abnormalities) tend to be a late finding and are not always accompanied by cardiovascular hemodynamic changes.

Treatment - In general, treatment of overdosage should be symptomatic and supportive. Cardiac arrhythmias and 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 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Doxepin binds with high affinity to the histamine H_1 receptor (Ki < 1 nM) where it functions as an antagonist. The exact mechanism by which doxepin exerts its sleep maintenance effect is unknown but is believed due to its antagonism of the H_1 receptor.

Pharmacodynamics

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.

Clinical Electrocardiography Study

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.

Pharmacokinetics

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

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.

Summary of Doxepin Pharmacokinetic Parameters in healthy volunteers following a Single Dose of 6 mg

Parameter (Unit)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng*h/mL)	T_{max} (h)	$t_{1/2}$ (h)
6 mg tablets	0.8864 (59.4) n=16	15.19 (69.1) n=16	3.5 (2.0–6.0) n=16	15.32 (31.3) n=16

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

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.

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.

STORAGE AND STABILITY

Keep SILENOR in a safe place away from children.

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

SPECIAL HANDLING INSTRUCTIONS

This drug does not require any special temperature storage conditions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SILENOR (doxepin HCl) 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 (3 and 6 mg) is supplied in individually sealed child-resistant blister packages contained in a cardboard outer carton, in pack sizes of 30 tablets or in bottles of 30, 100 and 500 tablets. The packaging is color-coded for each SILENOR tablet strength: blue package for the 3 mg strength and green for the 6 mg strength.

The SILENOR tablet formulations also contain the following non-medicinal ingredients: Microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, D&C lake yellow and FD&C lake blue.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

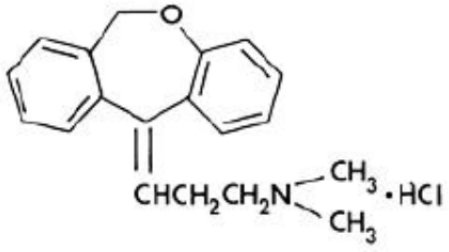
Proper name: doxepin hydrochloride

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

Molecular formula: $C_{19}H_{21}NO \cdot HCl$

Molecular mass: 315.84

Structural formula:



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

CLINICAL TRIALS

Study demographics and trial design

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.

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.

Withdrawal Effects

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.

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 – ie 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 Silenor discontinuation. However there was evidence of mild discontinuation effects on latency to persistent sleep (LPS) in the two nights following SILENOR discontinuation.

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), the symbol copying test (SCT), and a 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.

DETAILED PHARMACOLOGY

Pharmacodynamics

It is well established that doxepin is one of the most potent H_1 antagonist and has a substantial selectivity for H_1 receptors versus other CNS and peripheral targets (Cusack et al., 1994; Tatsumi et al., 1997). 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 (Van Laar et al., 2001).

Cardiovascular

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 IC50 of 6.5 ± 1.4 μM and native IKr with an IC50 of 4.4 ± 0.6 μM. (Duncan et al., 2007). 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). (Boeck et al., 1984, Constantine et al., 1964, David et al., 1984, Puisto et al., 1980, Tobis and Aronow, 1981).

Pharmacokinetics

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.

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.

Reproduction Toxicity

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)**.**

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PART III: CONSUMER INFORMATION

[Pr]**SILENOR™** doxepin HCl tablets

This leaflet is part III of a three-part "Product Monograph" published when SILENOR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SILENOR. Contact your physician or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SILENOR is a hypnotic (sleep) medicine that is used to treat people who have trouble staying asleep.SILENOR is not for use in children under 18 years of age.

What it does:

If you are prescribed sleep medications, you should consider both their benefits and risks. One important risk and limitation of Silenor is that it may affect your mental alertness particularly when not taken as prescribed. (see **Warnings and Precautions**)

When it should not be used:

Do not use SILENOR if you:

- have an eye problem called narrow angle glaucoma that is not being treated
- have difficulty urinating
- take a monoamine oxidase inhibitor (MAOI) medicine or have taken an MOAI in the last 14 days (2 weeks). Ask your healthcare provider if you are not sure if your medicine is a MAOI.
- are allergic (hypersensitive) to doxepin or any of the ingredients SILENOR contains (see **What the nonmedicinal ingredients are**)

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

What the medicinal ingredient is:

Doxepin hydrochloride

What the nonmedicinal ingredients are:

Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, D&C lake yellow and FD&C lake blue.

What dosage forms it comes in:

SILENOR tablets are available in two strengths, 3 mg and 6 mg.

WARNINGS AND PRECAUTIONS

Need to diagnose other existing conditions

Sleep problems can be a symptom of many physical and psychiatric disorders. Your physician will need to evaluate your medical history before initiating treatment with SILENOR. **Call your physician if your sleep problems get worse or do not get better within 7 to 10 days.** This may mean that there is another condition causing your sleep problem.

Complex sleep-related behaviours

There have been reports of people getting out of bed while not fully awake after taking sleeping pills and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. The unusual behaviour is more likely to occur when sleeping pills are taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. These activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), making and eating food, talking on the phone, having sex, sleep-walking, etc.

Important:
1. Do not take more SILENOR than prescribed.
2. Do not take SILENOR if you drink alcohol.
3. Talk to your physician about all the medicines, including over-the-counter medicines and herbal products. Your physician will tell you if you can take SILENOR with your other medicines.
4. You and people close to you should watch for the type of unusual behaviour described above. If you find out that you have done *any* such activities for which you have no memory you should call your physician immediately (see **Complex sleep-related behaviours)**.

Mental Alertness:

SILENOR may affect your ability to be alert. DO NOT DRIVE A CAR, or operate potentially dangerous machinery until you experience how this drug will affect you.

Worsening of Side Effects:
DO NOT CONSUME ALCOHOL WHILE TAKING SILENOR. Some medicines may also worsen side effects that some patients experience with SILENOR (see **Interactions with this medication**).

BEFORE you use SILENOR talk to your physician or pharmacist 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
- have an eye problem called narrow angle glaucoma that is not being treated
- have difficulty urinating
- are taking any other medicines, including over-the-counter medicines and herbal products.

- have any other medical conditions
- are pregnant, planning to become pregnant or you become pregnant while taking this medication. It is not known if SILENOR will harm your unborn baby.
- are breastfeeding or plan to breastfeed. SILENOR may pass into your milk and may harm your baby. You should not breast-feed while taking SILENOR.
- have any allergies to SILENOR or its ingredients or components of the container.

INTERACTIONS WITH THIS MEDICATION

Do not use SILENOR if you drink alcohol.

Do not use SILENOR along with other medications, over-the counter medicines or herbal products without first discussing this with your physician or pharmacist.

SILENOR may produce more pronounced side effects when co-administered with:

- alcohol
- other sleeping pills
- 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)

SILENOR may affect the way other medicines work, and other medicines may affects how SILENOR works. Especially tell your healthcare provider if you take:

- monoamine oxidase inhibitor (MAOI)
- cimetidine (an anti-acid medication)

PROPER USE OF THIS MEDICATION

How should I take SILENOR?

- Follow your physician's advice about how to take SILENOR, when to take it, and how long to take it. Do not take more SILENOR than prescribed for you.
- **Take SILENOR not more than 30 minutes before you get into bed.** After taking SILENOR, you should confine your activities to those necessary to prepare for bed.
- **Do not take SILENOR within 3 hours of a meal.** SILENOR may not work as well, or may make you sleepy the next day when taken with or right after a meal.
- **Do not take SILENOR unless you are able to get a full night of sleep (7-8 hours) before you must be active and functional again.**
- **Do not take SILENOR** if you drink alcohol.
- **Do not drive a car** or operate potentially dangerous machinery until you experience how SILENOR will affect you the next day.
- **Call your physician if your sleep problems get worse or do not get better within 7 to 10 days.** This may mean that there is another condition causing your sleep problem.
- SILENOR is not indicated for patients under 18 years of age. **Do not take SILENOR if you are under 18 years of age.**
- **Do not take SILENOR** if it is not prescribed for you.

Usual dose:

Adults
The recommended dose of SILENOR for adults is 6 mg once daily. The daily dose can be decresed to 3 mg if recommended by your physician.

Elderly
The recommended starting dose of SILENOR in elderly patients (≥ 65 years old) is 3 mg once daily. The daily dose can be increased to 6 mg, if recommended by your physician.

The daily dose prescribed by your physician should be of a maximum of 6 mg.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

You should only take SILENOR at bedtime. If you miss a dose, wait and take your next dose at your regular time the next night. Do not take 2 doses at the same time. Do not make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Serious side effects of SILENOR include getting out of bed while not being fully awake and do an activity that you do not know you are doing. (See **Warnings and Precautions, Complex Sleep-related behaviours**)

Call your physician right away if you have the above serious side effect or any other side effects that worry you while using SILENOR.

The most common side effects of SILENOR are tiredness, dizziness, nausea, headache and dry mouth.

How sleepy you are the day after you use one of sleeping pills depends on your individual response and on how quickly your body gets rid of the medication.

Do not drive or do any dangerous activities after taking SILENOR until you feel fully awake.

These are not all the side effects of SILENOR. Ask your physician or pharmacist for more information.

Call your physician for medical advice about side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your physician or pharmacist**		**Stop taking drug and call your physician or pharmacist**
		Only if severe	**In all cases**	
Common	Tiredness, dizziness, feeling "drugged"	√		
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			√

This is not a complete list of side effects. For any unexpected effects while taking SILENOR, contact your physician or pharmacist.

HOW TO STORE IT

- Store at room temperature between 15° and 30°C and protect from light.
- Keep SILENOR in a safe place away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.paladinlabs.com
or by contacting the sponsor, Paladin Labs Inc., at:
1-888-550-6060

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