These highlights do not include all the information needed to use Silenor safely and effectively. See full prescribing information for Silenor.

Silenor® (doxepin) tablets for oral administration

**INDICATIONS AND USAGE**

Silenor® (doxepin) tablets are indicated for the treatment of insomnia characterized by difficulties with sleep maintenance.

**CONTRAINDICATIONS**

- **Do not administer if patient is taking MAOIs or has used MAOIs within the past two weeks.**
- **Uncontrolled narrow angle glaucoma or severe urinary retention.**

**WARNINGS AND PRECAUTIONS**

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **CNS-depressant effects:** Use can impair alertness and motor coordination. Avoid engaging in hazardous activities such as operating a motor vehicle or heavy machinery after taking drug. (5.4) Do not use with alcohol. (5.4, 7.3)
- **Need to Evaluate for Comorbid Diagnoses:** Reevaluate if insomnia persists after 7 to 10 days of use. (5.1)
- **Abnormal thinking, behavioral changes, complex behaviors:** May include “sleep-driving” and hallucinations. Immediately evaluate any new onset behavioral changes. (5.2)
- **Depression:** Worsening of depression or suicidal thinking may occur. Prescribe the least amount feasible to avoid intentional overdose. (5.3)
- **CNS-depressant effects:** Use can impair alertness and motor coordination. Avoid engaging in hazardous activities such as operating a motor vehicle or heavy machinery after taking drug. (5.4) Do not use with alcohol. (5.4, 7.3)
- **Potential additive effects when used in combination with CNS depressants or sedating antihistamines.** Dose reduction may be needed. (5.4, 7.3, 5.4)
- **Patients with severe sleep apnea:** Silenor is ordinarily not recommended for use in this population. (8.7)

**ADVERSE REACTIONS**

- **The most common treatment-emergent adverse reactions, reported in ≥ 2% of patients treated with Silenor, are somnolence/sedation, nausea, and upper respiratory tract infection.** (8.1)

To report SUSPECTED ADVERSE REACTIONS, contact Perfinx Therapeutics, LLC. at 1-877-SILENOR (745-3667) and www.silenor.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- **MAOIs:** Silenor should not be administered in patients on MAOIs within the past two weeks. (4.2)
- **Cimetidine:** Increases exposure to doxepin. (7.2)
- **Alcohol:** Sedative effects may be increased with doxepin. (7.3, 5.4)
- **CNS Depressants and Sedating Antihistamines:** Sedative effects may be increased with doxepin. (7.4, 5.4)
- **Tolazamide:** A case of severe hyponychiaemia has been reported. (7.5)

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **Nursing Mothers:** Infant exposure via human milk. (8.3)
- **Pediatric Use:** Safety and effectiveness have not been evaluated. (8.4)
- **Geriatric Use:** The recommended starting dose is 3 mg. (8.5)
- **Use in Patients with Comorbid Illness:** Initiate treatment with 3 mg in patients with hepatic impairment or tendency to urinary retention. (8.6, 4.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 03/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

**1 INDICATIONS AND USAGE**

Silenor is indicated for the treatment of insomnia characterized by difficulties with sleep maintenance. The clinical trials performed in support of efficacy were up to 3 months in duration (see Clinical Studies (14)).

**2 DOSAGE AND ADMINISTRATION**

The dose of Silenor should be individualized.

**2.1 Dosing in 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.

**2.2 Dosing in the 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.

**2.3 Administration**

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 Clinical Pharmacology (12.3)).

The total Silenor dose should not exceed 6 mg per day.

**3 DOSAGE FORMS AND STRENGTHS**

Silenor is an immediate-release, oval-shaped, tablet for oral administration available in strengths of 3 mg and 6 mg. The tablets are blue (3 mg) or green (6 mg) and are debossed with 3 or 6, respectively, on one side and SP on the other. Silenor tablets are scored.

**4 CONTRAINDICATIONS**

- **Hypersensitivity:** Silenor is contraindicated in individuals who have shown hypersensitivity to doxepin HCl, any of its inactive ingredients, or other dibenzoxepines.

**5 WARNINGS AND PRECAUTIONS**

**1. Need to Evaluate for Comorbid Diagnoses**

Because sleep disturbances may be the presenting manifestation of a physical or/and psychiatric disorder, symptomatic treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Exacerbation of insomnia or the emergence of new cognitive or behavioral abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during treatment with hypnotics.

**2. Abnormal Thinking and Behavioral Changes**

Complex behaviors 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. These events can occur in hypnotic-naive as well as in hypnotic-experienced persons. Although behaviors 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 behaviors, as does the use of hypnotic 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. 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. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably.

**3. 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 in Silenor. Antidepressants increased the risk compared to placebo of suicidal thoughts and behaviors (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 can not be excluded.

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

**4. CNS Depressant Effects**

After taking Silenor, patients should confine their activities to those necessary to prepare for bed. Patients should avoid engaging in hazardous activities, such as operating a motor vehicle or heavy machinery, at night after taking Silenor, and should be cautioned about potential impairment in the performance of such activities that may occur the day following ingestion.

When taken with Silenor, the sedative effects of alcoholic beverages, sedating antihistamines, and other CNS depressants may be potentiated (see Warnings and Precautions (5.2) and Drug Interactions (7.3, 7.4)). Patients should not consume alcohol while taking Silenor (see Warnings and Precautions (5.2) and Drug Interactions (7.3, 7.4)). Patients should be cautioned about potential additive effects of Silenor used in combination with CNS depressants or sedating antihistamines (see Warnings and Precautions (5.2) and Drug Interactions (7.3, 7.4)).

**5 ADVERSE REACTIONS**

The following serious adverse reactions are discussed in greater detail in other sections of labeling:

- **Abnormal thinking and behavioral changes** (see Warnings and Precautions (5.2) and Drug Interactions (7.3, 7.4)).
- **Suicide risk and worsening of depression** (see Warnings and Precautions (5.3)).
- **CNS Depressant effects** (see Warnings and Precautions (5.4)).

**6.1 Clinical Trials Experience**

The pre-marketing development program for Silenor included doses up to 283 healthy subjects) participated in six randomized, placebo-controlled studies in patients with insomnia. The following serious adverse reactions are discussed in greater detail in other sections of labeling:
Cardiac Disorders: Rare: atrioventricular block, palpitations, tachycardia, ventricular extrasystoles.

Ear and Labyrinth Disorders: Rare: ear pain, hypacusis, motion sickness, tinnitus, tympanic membrane perforation.

Eye Disorders: Infrequent: eye redness, vision blurred; Rare: myopia, diplopia, eye pain, lacrimation decreased.

Gastrointestinal Disorders: Infrequent: abdominal pain, dry mouth, gastrointestinal reflux disease, vomiting; Rare: dyspepsia, constipation, gingival recession, haemachotysis, lip blisters.

Genitourinary and Reproductive System Disorders: Infrequent: dysuria, kidney pain, male reproductive system disorders, perineum, asthma, chest pain, fatigue; Rare: chills, gait abnormal, edema peripheral.

Hepatobiliary Disorders: Rare: hyperbilirubinemia.

Immune System Disorders: Rare: hypersensitivity.

Infections and Infestations: Infrequent: bronchitis, fungal infection, laryngitis, sinutitis, tooth infection, urinary tract infection, viral infection; Rare: cellulitis staphylococcal, eye infection, folliculitis, gastroenteritis viral, herpes zoster, infectious arthritis, influenza, laryngitis, long tract infection, onychomycosis, pharyngitis, pneumonitis.

Injury, Poisoning and Procedural Complications: Infrequent: back injury, fall, joint sprain; Rare: bone fracture, skin laceration.

Musculoskeletal and Connective Tissue Disorders: Infrequent: arthralgia, back pain, myalgia, neck pain, pain in extremity; Rare: joint range of motion decreased, muscle cramp, sensation of heaviness.

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): Rare: lung adenocarcinoma stage I, malignant melanoma.

Nervous System Disorders: Frequent: dizziness; Infrequent: dysarthria, lethargy, paramnesia, syncope; Rare: ageusia, ataxia, cerebrovascular accident, disturbance in attention, migraine, sleep paralysis, syncope vasovagal, tremor.

Psychiatric Disorders: Infrequent: abnormal dreams, adjustment disorder, anxiety, depression; Rare: confusional state, elevated mood, somnambulism, libido decreased, mania, nocturnal hallucinations.

Reproductive System and Breast Disorders: Rare: breast cyst, dysmenorrhea.

Renal and Urinary Disorders: Rare: dysuria, enuresis, hemoglobinuria, nocturia.

Respiratory, Thoracic and Medialinal Disorders: Infrequent: nasal congestion, pharyngolaryngeal pain, sinus congestion, wheezing; Rare: cough, crickles lung, nasopharyngeal disorder, rhinitis, dyspnea.

Skin and Subcutaneous Tissue Disorders: Infrequent: skin irritation; Rare: cold sweat, dermatitis, erythema, hyperhidrosis, pruritis, rash, rosacea.

Surgical and Medical Procedures: Rare: arthrodesis.

Vascular Disorders: Infrequent: pallor; Rare: blood pressure inadequately controlled, hemotoma, hot flush. In addition, the reactions below have been reported for other trocylics and may be idiosyncratic (not related to dose).

Allergic: photosensitization, skin rash.

Hematologic: agranulocytosis, eosinophilia, leukemia, purpura, thrombocytopenia.

7. DRUG INTERACTIONS

7.1. Cytochrome P450 Isozymes

Silenor is primarily metabolized by hepatic cytochrome P450 isozymes 3A4 (CYPC3A4) and 2D6, 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.

7.2. Cimetidine

Silenor exposure is doubled with concomitant administration of cimetidine, a nonselective inhibitor of CYP isozymes. A maximum dose of 3 mg is recommended in adults and elderly women who are co-administered with Silenor [see Clinical Pharmacology (12.4)].

7.3. Alcohol

When taken with Silenor, the sedative effects of alcohol may be potentiated [see Warnings and Precautions (5.2, 5.4)].

7.4. CNS Depressants and Sedating Antihistamines

When taken with Silenor, the sedative effects of sedating antihistamines and CNS depressants may be potentiated [see Warnings and Precautions (5.2, 5.4)].

7.5. Tolazamide

A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 g/day) 11 days after the addition of oral doxepin (75 mg/day).

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Category C

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 during pregnancy 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/day) was administered orally to pregnant rats during the period of organogenesis, developmental toxicity and Administration Study Conditions. Adverse reactions reported by subjects treated with Silenor.

Reactions in Long-term Placebo-Controlled Clinical Trials

Table 1 Incidence (%) of Treatment-Emergent Adverse Reactions in Long-term Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo</th>
<th>Silenor 1 mg</th>
<th>Silenor 3 mg</th>
<th>Silenor 6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System Disorders</td>
<td>Symomolence/Sedation</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Upper Respiratory Tract Infection/Nasopharyngitis</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Hypertension</td>
<td>0</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Includes reactions that occurred at a rate of ≥2% in any Silenor-treated group and at a higher rate than placebo.

The most common treatment-emergent adverse reaction in the placebo and each of the Silenor dose groups was somnolence/sedation.

8.2. Labor and Delivery

The effects of Silenor on labor and delivery in pregnant women are unknown.

8.3. Nursing Mothers

Doxepin is excreted in human milk after oral administration. There has been no report of adverse reactions occurring in the nursing infant whose mother was taking the higher dose of doxepin used to treat depression. Caution should be exercised when Silenor is administered to nursing women.

8.4. Pediatric Use

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

8.5. Geriatric Use

A total of 382 subjects who were ≥65 years and 86 subjects who were ≥75 years received Silenor in controlled clinical studies. No significant differences in treatment and adverse event effectiveness were observed between these subjects and younger adult subjects. Greater sensitivity of some older individuals cannot be ruled out.

Sleep-promoting drugs may cause confusion and confusion in the elderly. A starting dose of 3 mg is recommended in this population and evaluation prior to considering dose escalation is recommended [see Dosage and Administration (2.2)].

8.6. 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. [see Clinical Pharmacology (12.5)]

8.7. Use in Patients with Sleep Apnea

Silenor has not been studied in patients with obstructive sleep apnea. The capacity to depress ventilatory drive, precautions should be taken if Silenor is prescribed to patients with compromised respiratory function. In patients with severe sleep apnea, Silenor is ordinarily not recommended for use.

8.8. DRUG ABUSE AND DEPENDENCE

Doxepin is not a controlled substance.

8.9. Controlled Substance

Doxepin is not associated with abuse potential in animals or in human volunteers. The abuse potential of the drug is low and doxepin do not follow such patients closely, observing them for signs of misuse or abuse of doxepin (e.g., incrementation of dose, drug-seeking behavior).

8.10. Dependence

In a long-term study of adverse events observed during discontinuation of doxepin following chronic administration, no symptoms indicative of a withdrawal syndrome were observed. Thus, doxepin does not appear to produce physical dependence.

8.11. OVERDOSE

Doxepin is not administered for indications other than insomnia at doses 10- to 50-fold higher than the highest recommended dose of Silenor.

The symptoms and signs associated with doxepin use at doses several-fold higher than the maximum recommended dose (Excessive dose) of Silenor for the treatment of insomnia are described [see Overdosage (10.1)], as are signs and symptoms associated with higher multiples of the maximum recommended dose (Clinical Overdose) [see Overdosage (10.2)].
Concomitant use of hyperventilation and sodium bicarbonate alkalinization, using intravenous sodium bicarbonate should the best indication of the severity of an overdose. Serum during this period, extended monitoring is recommended. There hypotension, cardiac dysrhythmias and/or conduction blocks, and minimum of six hours of observation with cardiac monitoring should be established, and gastric decontamination should be initiated. A cardiac monitoring should be initiated immediately. The patient's rigidity, vomiting, hypothermia, hyperpyrexia.

overdose may include, but are not limited to: confusion, disturbed particularly in QRS axis or width, are clinically significant manifestations of doxepin critical overdose include: cardiac association with chlorpromazine).

alopecia, exacerbation of asthma, and hyperpyrexia (in inappropriate antidiuretic hormone secretion.

males, enlargement of breasts and galactorrhea in the female, gastrointestinal: numbness, paresthesias, extrapyramidal symptoms, seizures, hyperpyrexia (in

isomeric mixture of 1 propanamine, 3-dibenz\[ylidene-\(N,N\)-dimethyl-hydrochloride. It has the following structure:

Doxepin hydrochloride is a white crystalline powder, with a slight amine-like odor, that is readily soluble in water. It has a molecular weight of 315.84 and molecular formula of C19H21NO•HCl.

Each tablet includes the following inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, colloidal anhydrous silica, light anhydrous silicic acid, and magnesium stearate. The 3 mg tablet also contains FD&C Blue No. 1. The 6 mg tablet also contains FD&C Blue No. 1.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Doxepin binds with high affinity to the histamine H1 receptor (Ki < 1 nM) where it functions as an agonist. The exact mechanism by which doxepin exerts its sleep maintenance effect is unknown but is believed to be dissociative of the H1 receptor.

12.2. Pharmacodynamics

Cardiac Safety

In a thorough QTc prolongation clinical study in healthy subjects, doxepin had no effect on QT intervals or other electrocardiographic parameters after multiple daily doses up to 50 mg.

12.3. Pharmacokinetics

Absorption

The median time to peak concentrations (Tmax) of doxepin occurred at 3.5 to 5.0 hours post dose. Absorption of doxepin was almost complete, with mean bioavailability of approximately 90%.

Concomitant use of sucralfate and nasogastric tube feeding should be used to maintain the serum in the range of 7.4 to 7.55 mmol/L for patients with dysrhythmias and/or QRS widening. If the pH response is inadequate or should an intravenous line be established, and gastric decontamination should be initiated. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias, hyponatremia, and decreased creatinine clearance, and seizures is strongly advised. If signs of toxicity occur at any time during this period, extended monitoring is recommended. There are case reports of patients succumbing to fatal dysrhythmias late post overdose; therefore, patients have clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by administration of activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of an overdose. Serum acidosis, using intravenous sodium bicarbonate should be maintained to the serum in the range of 7.4 to 7.55 mmol/L for patients with dysrhythmias and/or QRS widening. If the pH response is inadequate or should an intravenous line be established, and gastric decontamination should be initiated. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias, hyponatremia, and decreased creatinine clearance, and seizures is strongly advised. If signs of toxicity occur at any time during this period, extended monitoring is recommended. There are case reports of patients succumbing to fatal dysrhythmias late post overdose; therefore, patients have clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Impairment of Fertility

In rats (10 mg/kg/day) are less than those in humans at the maximum recommended human dose of 6 mg/day.

13. NONCLINICAL TOXICOLOGY


There is no evidence of carcinogenic potential when doxepin was administered orally to hamsters and mice.

Mutagenesis

Doxepin was negative in in vitro bacterial reverse mutation, chromosome aberration (in human lymphocytes) and in vivo (micronucleaus) assays.

Impairment of Fertility

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.

14. CLINICAL STUDIES

14.1. Controlled Clinical Trials

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 insomnia (N=895) or transient (N=528) insomnia. Silenor was evaluated at doses of 1 mg, 3 mg, and 6 mg relative to placebo in insomniac (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 superior to placebo (N=185) or trazodone (N=36).

Silenor 3 mg and 6 mg were superior to placebo on objective WASO. 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.

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 insomniac and outpatient settings in elderly subjects (N=240) with chronic insomnia. Silenor 3 mg was superior to placebo on objective 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.

Insomnia

On subjective sleep latency, Silenor 6 mg was superior to placebo. Silenor 6 mg was superior to placebo on objective WASO and subjective WASO. On subjective sleep latency, Silenor 6 mg was superior to placebo.

Transient Insomnia

Healthy adult subjects (N=565) experiencing transient insomnia 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 25-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 Tyser’s Symptom Checklist. However, reports of anxiety and insomnia occurring 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 in adults with chronic insomnia. Silenor 3 mg and 6 mg showed no evidence of rebound effect.
16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied
Silenor 3 mg tablets are oval shaped, blue, identified with debossed markings of “3” on one side and “SP” on the other, and are supplied as:

- NDC 42847-103-30 Bottle of 30
- NDC 42847-103-10 Bottle of 100
- NDC 42847-103-50 Bottle of 500
- NDC 42847-103-03 Blister trade pack of 30

16.2. Storage and Handling
Store at controlled room temperature 20°- 25°C (68°- 77°F), protected from light.

17. PATIENT COUNSELING INFORMATION
Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with hypnotics, should counsel them in appropriate use, and should instruct them to read the accompanying Medication Guide (see Medication Guide (17.4)).

17.1. 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 (5.2, 5.4) and Drug Interactions (7.3, 7.4)). 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.

17.2. 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.

17.3. 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 with or immediately after a meal (see Dosing and Administration (2.3)). Advise patients NOT to take Silenor when drinking alcohol (see Warnings and Precautions (5.2, 5.4) and Drug Interactions (7.3)).

17.4. Medication Guide

MEDICATION GUIDE
SILENOR® (SI-leh-nor) Tablets
(doxepin)

Read this Medication Guide before you start taking SILENOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SILENOR?
After taking SILENOR, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medications that make you sleepy with SILENOR. Reported activities include:
- driving a car ("sleep driving")
- making and eating food
- talking on the phone
- having sex
- sleep-walking

Call your healthcare provider right away if you find out that you have done any of the above activities after taking SILENOR.

Important:
1. Take SILENOR exactly as prescribed
   - Do not take more SILENOR than prescribed.
   - Take SILENOR 30 minutes before bedtime. After taking SILENOR, you should only do activities needed to get ready for bed.
2. Do not take SILENOR:
   - with alcohol
   - if you take other medicines that can make you sleepy. Talk to your healthcare provider about all of your medicines. Your healthcare provider will tell you if you can take SILENOR with your other medicines
   - if you cannot get a full night of sleep before you must be active again

What is SILENOR?
SILENOR is a hypnotic (sleep) medicine that is used to treat people who have trouble staying asleep.

Who should not take SILENOR?
Do not take SILENOR if you:
- have a monoamine oxidase inhibitor (MAOI). See "Who should not take SILENOR?"
- have a history of drug or alcohol abuse or addiction
- have any of the following medical conditions:
  - have a history of glaucoma or urinary retention
  - have had severe anemia
  - have kidney or liver problems
  - have a history of drug or alcohol abuse or addiction
  - have a problem called narrow angle glaucoma that is not being treated
  - have trouble urinating
  - are allergic to any of the ingredients in SILENOR

See the end of this Medication Guide for a complete list of ingredients in SILENOR.

Talk to your healthcare provider before taking this medicine if you have any of these conditions. It is not known if SILENOR is safe and effective in children.

What should I tell my healthcare provider before taking SILENOR?
Before you take SILENOR, tell your healthcare provider if you:
- See "Who should not take SILENOR?"
- have a history of depression, mental illness, or suicidal thoughts
- have severe anemia
- have kidney or liver problems
- have a history of drug or alcohol abuse or addiction
- have a history of glaucoma or urinary retention
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if SILENOR will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breast-feeding or planning to breast-feed. SILENOR can pass into your milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take SILENOR. You should not breast-feed while taking SILENOR.

Tell your doctor about all of the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.

SILENOR and other medicines may affect each other causing side effects. SILENOR may affect the way other medicines work, and other medicines may affect how SILENOR works. Especially tell your healthcare provider if you take:
- a monoamine oxidase inhibitor (MAOI). See "Who should not take SILENOR?"
- cimetidine (Tagamet) or other medicines that can affect certain liver enzymes
- certain allergy medicines (antihistamines) or other medicines that can make you sleepy or affect your breathing
- the diabetes medicine tolazamide

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take SILENOR?
- Take SILENOR exactly as your healthcare provider tells you to take it.
- Your doctor will tell you how many SILENOR to take and when to take them.
- Your doctor may change your dose if needed.
- Take SILENOR within 30 minutes of bedtime. 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 if taken with or right after a meal.
- Do not take SILENOR unless you are able to get a full night of sleep before you must be active again.
- Call your doctor 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.
- If you take too much SILENOR, call your doctor or get medical help right away.

What should I avoid while taking SILENOR?
- You should not drink alcohol while taking SILENOR. Alcohol can increase your chances of getting serious side effects with SILENOR.
- You should not drive, operate heavy machinery, or do other dangerous activities after SILENOR.

You may still feel drowsy the next day after taking SILENOR. Do not drive or do other dangerous activities after taking SILENOR until you feel fully awake.

What are the possible side effects of SILENOR?
SILENOR can cause serious side effects including:
- See "What is the most important information I should know about SILENOR?"

The most common side effect of SILENOR is drowsiness or tiredness.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SILENOR. For more information ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store SILENOR?
- Store SILENOR between 8° and 77° F (20° to 25°C).
- Keep SILENOR in a tightly closed container, and away from light. Safely throw away medicine that is out of date or no longer needed.
- Keep SILENOR and all medicines out of the reach of children.

General Information about SILENOR
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SILENOR for a condition for which it was not prescribed. Do not share SILENOR with other people, even if you think they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SILENOR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about SILENOR that is written for healthcare professionals.

For more information, contact Pernix Therapeutics, LLC. at 1-877-SILENOR (745-3687) or visit http://www.silenor.com.

What are the ingredients in SILENOR?
Active Ingredient: doxepin hydrochloride
Inactive Ingredients: Microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The 3 mg tablet also contains FD&C Blue No. 1. The 6 mg tablet also contains FD&C Yellow No. 10 and FD&C Blue No. 1.

Manufactured for:
Pernix Therapeutics, LLC
Morristown, NJ 07960 USA

This Medication Guide has been approved by the U.S. Food and Drug Administration.