

## NEW DRUG UPDATE

<b>Drug Name:</b>	doxepin
<b>Trade Name (Manufacturer):</b>	Silenor® (Somaxon)
<b>Form:</b>	Tablet
<b>Strength:</b>	3 mg and 6 mg
<b>FDA Approval:</b>	March 17, 2010
<b>Market Availability:</b>	Anticipated 2Q2010
<b>FDA Approval Classification:</b>	Standard review
<b>Classification:</b>	Specific Therapeutic Class (HIC3): Sedative Hypnotics (H2E)

**Indication<sup>1</sup>:** Doxepin (Silenor) tablets are indicated for the treatment of insomnia characterized by difficulties with sleep maintenance.

### **Contraindications/Warnings:**

Silenor is contraindicated in patients with hypersensitivity to doxepin, inactive ingredients within the medication, or other dibenzoxepines. Patients with untreated narrow angle glaucoma or severe urinary retention should not use Silenor.

Patient's insomnia and co-morbid disease states should be reassessed if insomnia exists for more than seven to ten days. Abnormal thinking, behavioral changes, and complex behaviors including "sleep-driving" and hallucinations have been associated with Silenor and should be evaluated immediately. Depression and suicidal thinking have also been linked to Silenor. CNS depression affecting alertness and motor coordination have occurred, therefore patients should use caution. The use of Silenor in patients with sleep apnea is not recommended.

### **Drug Interactions:**

Concomitant administration of Silenor and alcohol, CNS depressants, and sedative antihistamines has shown increased sedative effects. Severe hypoglycemia has been reported with the simultaneous use of tolazamide. Using Silenor and cimetidine together has caused an increased exposure to Silenor. Patients should not have used a Monoamine Oxidase Inhibitor (MAOI) medication within the last 14 days.

### **Common Adverse Effects:**

During clinical trials, adverse reactions occurring in greater than or equal to two percent of patients and greater than the incidence of those treated with placebo, respectively, included: somnolence/sedation (6 to 9 percent versus 4 percent), upper respiratory tract infection/nasopharyngitis (2 to 4 percent versus 2 percent), gastroenteritis (0 to 2 percent versus 0 percent), nausea (2 percent versus 1 percent), and hypertension (less than 1 percent to 3 percent versus 0 percent).

### **Special Populations:**

**Pediatrics:** The safety and effectiveness of Silenor in pediatric patients have not been established.

**Pregnancy:** Pregnancy Category C.

**Geriatrics:** Clinical studies with 448 patients who were 65 years of age or older received Silenor and no overall differences in safety or effectiveness were observed between these patients and younger adults.

**Renal Impairment:** The effects of using Silenor in patients with renal impairment have not been evaluated.

**Hepatic Impairment:** Patients with hepatic impairment may display higher Silenor concentrations than healthy patients. Patients with hepatic impairment should initiate treatment at 3 mg daily and monitor for adverse daytime effects.

**Dosages:** The recommended adult dose of Silenor is 6 mg once daily. However, the dosage should be individualized and a 3 mg once daily dose may be appropriate for some patients. Silenor should be taken 30 minutes before bedtime and not taken within three hours of a meal. Patients should not take more than 6 mg daily.

**Clinical Trials:** A literature search was performed using “doxepin” and “insomnia”.

In a randomized, double-blind, multi-center, placebo-controlled, four-period crossover, dose-response study was performed to compare doxepin (1 mg, 3 mg, and 6 mg) to placebo for the treatment of chronic primary insomnia. Study inclusion and exclusion criteria were used to assess the eligibility of 237 patients which resulted in 184 patients who qualified for the second selection step. A polysomnography (PSG) was performed on the 184 patients to determine whether they met PSG criteria. Patients were required to have delay to persistent sleep (greater than 10 minutes), a wake time during sleep (greater than 60 minutes with no night less than 45 minutes), and sleep time totaling greater than 240 minutes but less than 410 minutes. Sixty-seven patients entered the study with one patient dropping out due to anxiety possibly related to doxepin. The study concluded that all three doses showed statistically significant improvements in wake after sleep initiation, total sleep time, and sleep efficiency compared to placebo. The medication was well tolerated, had no significant hangover effects, and was efficacious in improving sleep in patients with chronic primary insomnia.<sup>2</sup> This study was fully funded by the manufacturer.

**Other Drugs Used for Condition:** Other common oral drugs indicated for the treatment of insomnia include estazolam (Prosom<sup>®</sup>), flurazepam (Dalmane<sup>®</sup>), quazepam (Doral<sup>®</sup>), temazepam (Restoril<sup>®</sup>), triazolam (Halcion<sup>®</sup>), chloral hydrate (Somnote<sup>®</sup>), eszopiclone (Lunesta<sup>®</sup>), zolpidem (Ambien<sup>®</sup>/Ambien CR<sup>®</sup>), ramelteon (Rozerem<sup>®</sup>), and zaleplon (Sonata<sup>®</sup>).

**Place in Therapy:** Many of the agents indicated for use in the treatment of insomnia are safe, effective, and available in generic forms which are commonly less expensive when compared to brand-name products. The American Academy of Sleep Medicine (AASM) 2008 guidelines suggest a first time therapy of short or intermediate-acting Benzodiazepine Receptor Agonistic Modulators (BRAM) including eszopiclone, triazolam, zaleplon, and zolpidem. Patients who prefer not to use DEA scheduled medications or who have a history of drug abuse may benefit from ramelteon. The AASM states that no BRAM is preferred, selection of treatment is individualized, and patients who fail initial treatment should try another BRAM or ramelteon. Patients unsuccessfully treated with BRAMS may benefit from a sedating low-dose antidepressant such as trazodone, mirtazapine, doxepin, amitriptyline, and trimipramine.<sup>3</sup> When used alone, antidepressants have not shown strong evidence of efficacy and the AASM states that one product is not preferred over another.<sup>4, 5, 6, 7, 8</sup> For patients whose insomnia persists, a

combination therapy comprised of BRAM and an antidepressant may be attempted. The AASM indicates no studies have been performed to examine the efficacy of this combination but have noted clinical experiences suggest the treatment is generally safe and effective. Other therapies include anti-epileptics, atypical antipsychotics, and over-the counter (OTC) medications including sedating antihistamines and herbals. However, the AASM has discouraged the use of these alternative therapies due to safety, side effects, or lack of proven efficacy. Furthermore, the AASM does not recommend the use of barbiturates, chloral hydrate, or “non-barbiturate, non-benzodiazepine” despite being FDA approved to treat insomnia due to significant side effects, tolerance, and dependence.<sup>9</sup>

**Suggested Utilization Management:**

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Sedative Hypnotics
<b>Clinical Edit</b>	Prior authorization should be required if it is determined that this product will be non-preferred in the appropriate PDL class as indicated above. No MAOI within 14 days.
<b>Quantity Limit</b>	1 tablet daily; May want to consider a duration of therapy limit
<b>Duration of Approval</b>	TBD
<b>Drug to Disease Hard Edit</b>	Patient should have diagnosis of insomnia.
<b>Retro-DUR</b>	Yes
<b>Provider Profiling</b>	No
<b>Coding</b>	Please contact Mary Roberts IF there are coding questions

**References**

<sup>1</sup> Silenor [package insert]. San Diego, CA. Somaxon. March 2010.  
<sup>2</sup> Roth T, Rogowski R, Hull S, Schwartz et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep* 2007; 30(11):1555-1561.  
<sup>3</sup> Schutte-Rodin S, Broch L, Buysse D, et al. Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine* 2008;4(5):487-503.  
<sup>4</sup> Hajak G, Rodenbeck A, Voderholzer U, et al. Doxepin in the treat of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. *J Clin Psychiatry* 2001;62:453-63.  
<sup>5</sup> D, Voderholzer, U, Cohrs S, et al. Trimipramine in primary insomnia: results of a polysomnographic double-blind controlled study. *Pharmacopsychiatry* 2002;35:165-74.  
<sup>6</sup> Mendelson W. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry* 2005;66:469-76.  
<sup>7</sup> J, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. *Hum Psychopharmacol* 1998;13:191-8.  
<sup>8</sup> A, DeMartinis NA 3rd, McNally DP, Gary EM, Cormier JL, Gary KA. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures with major depression and insomnia. *J Clin Psychiatry* 2003;64:1224-9.  
<sup>9</sup> Schutte-Rodin S, Broch L, Buysse D, et al. Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine* 2008;4(5):487-503.