Somaxon®
Pharmaceuticals

April 7, 2010

Dear Carlat Psychiatry:

This letter is in response to your posted comments about Silenor in the "Carlat Psychiatry Report Practice Alert; March 24, 2011."

In your article you have recommended off label use for doxepin HCl 10 mg for the treatment of insomnia. First and foremost, we believe it is important to provide you with the medical, scientific and regulatory reasons why it is inappropriate to make that recommendation. We have attached as an exhibit a letter prepared by our Medical Affairs Department setting forth such reasons and concluding that there is no evidence-based medical justification for substituting 10 mg doxepin HCl for Silenor. A brief summary of the reasons is as follows:

- the safety and efficacy of doses higher than 6 mg have never been evaluated or approved by the FDA for the treatment of insomnia, and our FDA-approved labeling states that doses of doxepin above 6 mg should not be used for the treatment of insomnia;
- doxepin capsules containing 10 mg or more of doxepin are not AB-rated or substitutable for Silenor tablets;
- our PK modeling work shows that there may be a substantial increase in bioavailability for the 10 mg capsule vs. Silenor, including plasma concentrations the next morning for the 10 mg capsule being higher than the maximum nighttime plasma concentrations of Silenor;
- the FDA-approved labeling for Silenor contains instructions for the safe dosing and administration of Silenor for the treatment of insomnia, and there are no such instructions in the labeling for generic versions of higher-dose doxepin capsules (the instructions for those capsules relate only to usage for depression and anxiety);
- all higher-dose generic doxepin capsules, including the 10 mg capsules, have a black-box warning in their FDA-approved labeling relating to increased risk of suicidality in children, adolescents and young adults (the Silenor label does not have any black-box warnings);
- in our clinical studies of Silenor, adverse event reports of somnolence and sedation were higher for the 6 mg dose than for the 3 mg dose, and further increases in dose would be expected to result in a greater increase; and

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- our clinical studies revealed significant increases in plasma concentrations of Silenor when it is taken in the presence of other drugs that are CYP P450 inhibitors, and increasing the dosage of doxepin would be expected to exacerbate this effect for patients on such other drugs.

We also want to remind you that we hold exclusive rights to two issued U.S. patents covering the use of doxepin in dosage ranges from 0.5 mg to 20 mg for the treatment of insomnia. Specifically, U.S. patent number 5,502,047 covers the use of doxepin in dosage ranges from 0.5 mg to 20 mg for the treatment of chronic insomnia, and U.S. patent number 6,211,229 covers the use of doxepin in dosage ranges from 0.5 mg to 20 mg for the treatment of non-chronic insomnia.

Your March 24, 2011 recommendations regarding the off label use of 10 mg of doxepin in the "Carlat Psychiatry Report Practice Alert" constitute an inducement to infringe these patents. Under U.S. patent law, one who actively induces infringement is liable as an infringer to the same extent as one who directly infringes a patent.

In order to ensure that physicians and patients are not provided with inappropriate medical advice (as well as to ensure that our patents are not infringed), we would like for you to cease providing advice regarding the use of doxepin formulations other than Silenor for the treatment of insomnia, including advice of the type contained in the "Carlat Psychiatry Report Practice Alert" on March 24.

Please contact me if you would like to discuss this further. Thank you.

Very truly yours,

Matthew W. Onaitis
General Counsel
Somaxon Pharmaceuticals, Inc.

Exhibit A

Is the 10 mg Doxepin Capsule a Suitable Substitute for the Silenor® 6 mg Tablet?

The question has arisen as to whether or not a generic version of doxepin, in particular the 10 mg capsule, might be substituted for Silenor® tablets in patients prescribed Silenor by their health care provider for the treatment of sleep maintenance insomnia. This document describes the reasons why such a substitution is not advisable based on regulatory, scientific and medical grounds.

It is important to emphasize that Silenor represents the only dose range and formulation of doxepin approved to treat sleep maintenance insomnia. The use of 3 mg and 6 mg Silenor tablets is patent-protected for the treatment of sleep maintenance insomnia, and at present no other dose or formulation may be labeled for this indication. Moreover, the Silenor dose range and formulation do not overlap with any other currently approved doxepin product. Although doses of doxepin higher than those contained in Silenor have been the subject of studies in insomnia patients, these higher doses have not been shown to be safe and effective for the treatment of insomnia. Because the doxepin doses in Silenor differ from those of other doxepin-containing products, branded and generic doxepin capsules containing doses of 10 mg and higher are not "AB rated" to substitute for Silenor tablets. This designation refers to a scientific process used to ensure that one form of a drug will have the same therapeutic effect and safety profile as another form of the same drug.

The FDA classifies as AB-rated, or therapeutically equivalent, to products that:

- Are safe and effective;
- Are pharmaceutical equivalents; i.e., they contain the same amount of drug in the same dosage form
- Meet accepted standards of strength, quality, purity, and identity;
- Are bioequivalent by *in vitro* or *in vivo* standards
- Are adequately labeled
- Are manufactured in compliance with Current Good Manufacturing Practice regulations

(Food and Drug Administration, 2010)

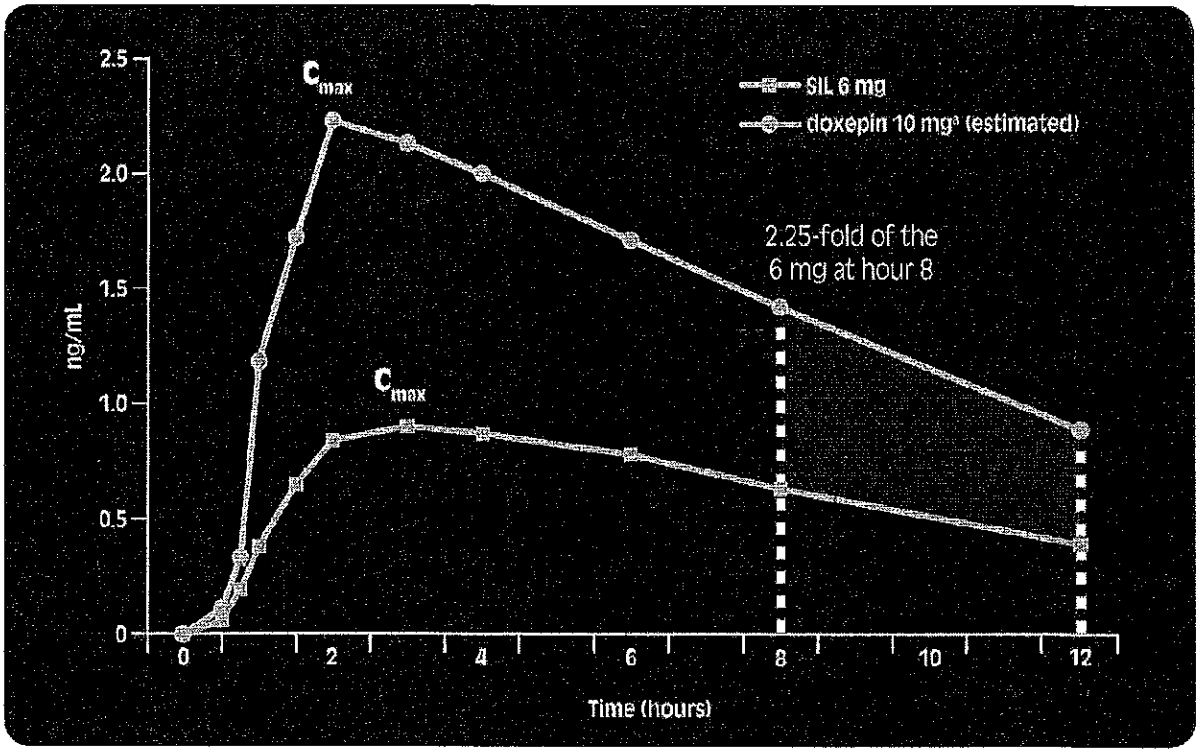
The characteristics of Silenor in drug dissolution studies (performed *in vitro*) and in human pharmacokinetic studies (performed *in vivo*) are important in determining the potential for an AB rating and for highlighting important differences between Silenor tablets and doxepin capsules. Drug dissolution studies show how quickly and completely a solid dosage product releases its active ingredient into solution, thereby making it available for absorption by the gastrointestinal system. Dissolution studies performed by Somaxon demonstrated that Silenor tablets are not identical to generic doxepin capsules (Somaxon data on file). This finding has important implications to the pharmacokinetic performance of the two dosage forms.

What does this mean when comparing the 6 mg Silenor tablet to generic 10 mg doxepin capsules? It is important to emphasize that the difference in dosage strength (67%) would preclude the 10 mg capsule as a candidate for bioequivalence (and therefore an AB rating) based on the FDA criteria, and predict a substantial difference in plasma exposure.

Nevertheless, in order to determine *relative* bioavailability of Silenor in comparison to Sinequan® (doxepin capsules), Somaxon has studied the human pharmacokinetic properties of the two dosage forms. In this trial, subjects were administered either a 6 mg Silenor tablet or a 50 mg Sinequan capsule, and on a later date were given the treatment they did not receive the first time (Somaxon data on file). The doxepin plasma concentrations were measured at several time points after dosing, which allowed the estimation of key pharmacokinetic parameters. The performance of Silenor tablets was compared to that of doxepin capsules by dose-normalization, which takes into account the differences in dosage strength. The results demonstrated that Silenor tablets do not produce the same pharmacokinetic profile as doxepin capsules, meaning that the maximum concentration (C_{max}) and total exposure (AUC) are not similar enough to conclude that the two forms of the drug are interchangeable, even when taking dose differences into account. On a per-milligram basis, approximately 30% less doxepin is absorbed from Silenor tablets than from doxepin capsules, leading to lower C_{max} and AUC values. This finding underscores important differences in how the two dosage forms are formulated; Silenor tablets represent a unique and proprietary solid formulation of doxepin with novel excipients (inactive ingredients that aid in crafting the absorption profile of doxepin) not contained in doxepin capsules.

In a supplemental analysis of the study described above, the pharmacokinetic parameters observed with the 50 mg doxepin capsule were used to estimate the same parameters expected with a 10 mg capsule. It is important to note that 10 mg doxepin was not included in this study, but estimated from the results of the 50 mg doxepin study. As such, the actual relative bioavailability of 10 mg doxepin may vary from the estimated results presented in these data. The results of this analysis suggest that the difference in drug exposure between 6 mg Silenor tablet and 10 mg doxepin capsule, which, as noted above, would be expected to be 67% simply by comparing the nominal dosage strengths, may be even larger. Specifically, the C_{max} value estimated for the 10 mg capsule is 2.5-fold that of the value determined for the Silenor 6 mg tablet (Figure 1). Eight hours after dosing, approximately the time that a person would awaken after an evening dose, it is estimated that the doxepin plasma concentration after dosing with a 10 mg capsule would be more than 1.6-fold that of the C_{max} associated with the Silenor 6 mg tablet, which is observed at approximately 3 hours after dosing (Figure 1). That is to say, plasma concentrations *the next morning* on a 10 mg capsule would be expected to be higher than the highest nighttime concentrations observed with the 6 mg Silenor tablet. Similarly, 12 hours after administration of a 10 mg capsule it is estimated that there would be approximately the same doxepin plasma concentration as observed with the 6 mg Silenor tablet at C_{max}. These results suggest potentially clinically significant differences in pharmacokinetic performance between 6 mg Silenor tablets and 10 mg doxepin capsules. A precise pharmacokinetic profile is especially important for insomnia drugs, because of the narrow window of time (i.e. time in bed) for which clinically significant exposures to the drug are intended.

Figure 1. Mean Plasma Concentrations of Silenor 6 mg vs. Estimated Doxepin 10 mg



[a]Data adapted from a randomized, open-label, 2-way crossover daytime study to assess the relative bioavailability of Silenor (doxepin) 6 mg tablets compared to doxepin 50 mg capsules in healthy subjects (N=24). PK blood samples were collected pre-dose and up to 96 hours post-dose to evaluate AUC and C_{max}. The results demonstrated that Silenor® tablets do not produce the same pharmacokinetic profile as doxepin capsules, meaning that the maximum concentration (C_{max}) and total exposure (AUC) are not similar enough to conclude that the two forms of the drug are interchangeable, even when taking dose differences into account.
10 mg doxepin was not included in this study. The actual relative bioavailability of 10 mg doxepin may vary from the estimated results presented in these data. 10 mg doxepin is not an approved dose for the treatment of insomnia.
Source: Somaxon data on file.

Silenor is a potent histamine H_1 receptor antagonist with much higher affinity for this site than for other pharmacological targets, and this activity is thought to mediate its beneficial effects and favorable safety profile at low doses in insomnia patients. Silenor was the subject of a rigorous program to evaluate its safety and efficacy, including 12 clinical studies (six Phase 1, two Phase 2, and four Phase 3 studies) in over 1000 subjects. These studies demonstrated clinical efficacy and supported a positive risk-benefit analysis of 3 mg and 6 mg Silenor tablets for the treatment of sleep maintenance insomnia. The Silenor clinical program formed the basis of the approved package insert, which contains guidance for prescribers that is unique to the doses and indication for which Silenor is approved, and specifically limits the total daily dose to 6 mg. From an efficacy perspective, Silenor product labeling provides specific dosing and administration recommendations with respect to use in sleep maintenance insomnia patients, which other forms of doxepin do not. Other forms of doxepin are approved for the treatment of depression and anxiety, and the corresponding prescribing information provides guidance only for these disorders. Table 1 illustrates the differences in approved indications between Silenor tablets and doxepin capsules.

Table 1. Indication Statements for Doxepin-containing Medications

Sinequan® (Doxepin Capsules)	Silenor® tablets
SINEQUAN is recommended for the treatment of: 1. Psychoneurotic patients with depression and/or anxiety. 2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol). 3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly). 4. Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders.	Silenor is indicated for the treatment of insomnia characterized by difficulty with sleep maintenance. The clinical trials performed in support of efficacy were up to 3 months in duration

Source: Silenor® and Sinequan® U.S. prescribing information

Moreover, doxepin capsules approved for depression and anxiety are accompanied by warnings and precautions that do not apply to Silenor, including a boxed warning ("black box") for suicidality. Table 2 illustrates a qualitative difference in warnings regarding suicidality between Silenor tablets and doxepin capsules.

Table 2. Suicidality warnings for doxepin-containing products (Emphasis Added)

Sinequan® (Doxepin Capsules) [Boxed Warning]	Silenor® tablets
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. **Anyone considering the use of Sinequan or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.** Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Sinequan is not approved for use in pediatric patients.	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 thinking and behavior (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 a particular 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.

Source: Silenor® and Sinequan® U.S. prescribing information

Use of doxepin at doses higher than 6 mg for the treatment of insomnia is not recommended for both safety and efficacy reasons. Results from the Silenor clinical trials demonstrated only a modest increase in mean sleep maintenance efficacy when the dose is increased from 3 mg to

6 mg. The dose of Silenor should be individualized. The recommended starting dose of Silenor for adults is 6 mg once daily. A 3 mg dose once daily dose may be appropriate for some patients, if clinically indicated. 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 total daily dose of Silenor should not exceed 6 mg. Thus, increasing the doxepin dose beyond 6 mg would not be expected to yield additional benefits, and may increase its risks, as described below.

In Silenor clinical studies with the 3 mg and 6 mg doses, the most common adverse event observed was somnolence/sedation, which increased in incidence from 6% at 3 mg to 9% at 6 mg (versus 4% for placebo). Further increases in dose would be expected to result in an even greater incidence of somnolence/sedation. For other adverse events, incidences after Silenor treatment were consistently low and not clinically significant. In contrast, doses of doxepin above 6 mg are associated with a number of dose-dependent adverse events, including anticholinergic effects (e.g., constipation and dry mouth) and effects on vital signs and electrocardiographic variables. However, no such findings were observed with the approved Silenor doses when compared to placebo.

Another standard approach to study the untoward effects of an insomnia medication is to examine human psychomotor performance the next morning after dosing. In one Silenor efficacy study, measures of psychomotor residual effects (i.e., "hangover") the 6 mg dose produced modest, though statistically significant, disturbances the morning after dosing. Such effects were not observed in long-term trials at the 3 mg dose. This dose-dependent relationship suggests the potential for even larger disruptions at doses greater than 6 mg.

Doxepin is subject to drug-drug pharmacokinetic interactions that may result in increased doxepin exposures. Doxepin is metabolized primarily by hepatic cytochrome P450 (CYP P450) enzymes 2D6 and 2C19. Clinical studies conducted by Somaxon have shown that doxepin plasma concentrations can be increased by as much as 2-fold after co-administration with a CYP P450 inhibitor. These findings suggest the potential for even greater absolute doxepin plasma concentrations if a higher dose of doxepin was prescribed and taken concomitantly with a CYP inhibitor. As a result, the probability of adverse consequences associated with doses above the approved Silenor dose range may be increased.

Considering what has been learned about the safety and efficacy of doxepin at low doses, there can be no evidence-based justification for substituting a higher dose of doxepin for the recommended Silenor doses in the treatment of sleep maintenance insomnia. Sound clinical judgment would invariably lead to the use of the lowest effective dose, thereby maximizing the tolerability and safety margin of the product. The studies conducted by Somaxon provide compelling evidence that the difference between 6 mg Silenor tablets and 10 mg doxepin capsules is not trivial from regulatory, pharmacokinetic and safety perspectives, and the 10 mg dose is unlikely to confer any additional benefits beyond those at the approved dose range. The only remaining justification for generic substitution is cost. However, with the co-pay assistance program available for Silenor --which can save patients up to $300 through 2011, up to $25 per prescription--most commercially insured patients will discover that their out-of-

pocket expense is less than $1 per day. This represents a more than adequate trade-off for the advantages of using branded Silenor for their sleep maintenance insomnia.

References

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