

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022036Orig1s000

OTHER ACTION LETTERS



NDA 022036

COMPLETE RESPONSE

Somaxon Pharmaceuticals, Inc.
3721 Valley Centre Drive, Suite 500
San Diego, CA 92130

Attention: Brian Dorsey
Vice President, Product Development

Dear Mr. Dorsey,

Please refer to your new drug application (NDA) dated January 31, 2008, received January 31, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Silenor (doxepin hydrochloride) 1mg, 3mg, and 6 mg Tablets.

We acknowledge receipt of your amendments dated June 4, 2009 and December 1, 2009.

The June 4, 2009 amendment constituted a complete response to our February 25, 2009 action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

As you know, as described in our Complete Response letter of February 5, 2009, we had concluded that you had not presented substantial evidence of effectiveness for Silenor as a treatment for insomnia characterized by difficulty maintaining sleep, based primarily on our finding that you had not documented a robust finding on a subjective measure of sleep maintenance. Specifically, in Study 501, there were no statistically significant differences between Silenor 6 mg and placebo on Nights 15 and 29, primary timepoints specified in the protocol at which subjective responses would be tested.

In your response to the CR letter, you primarily rely on the results of a Mixed Model Repeated Measures (MMRM) analysis of Study 501. Your contention that it is appropriate to analyze the trial with this method (and thereby rely on the average treatment effect over the entire duration of the trial to represent the treatment difference at the end of the trial) is based on a showing that there is no treatment by time interaction. In your view, you have ruled out any treatment by time interaction because the p-value for this term was not significant at the p=0.10 level.

Critically, we do not believe that a significance test can adequately establish that no interaction is present. We believe that such a finding can only be established by formal equivalence testing.

Furthermore, this study was not powered to detect a treatment by time interaction, and the power to do so in this trial was very low. Specifically, the power to detect an interaction between treatment and time at a significance level of 0.05, assuming the observed differences in treatment effect between Nights 1, 15, and 29 on subjective WASO are true, is 43%. In our view, therefore, the failure to reject the hypothesis of no interaction does not establish that, in fact, there is no important treatment by time interaction.

Inspection of the data also suggests that the pattern of treatment differences over time is not consistent. If we consider all data points except the final day 30, there appears to be a decrease in treatment effect. Further, the difference in the estimate of the treatment effect between Nights 29 and 30 is considerable (indeed, the difference between the treatment differences at Nights 29 and 30 is nominally significant, at $p < 0.011$). This makes any reliable estimate of the treatment effect at that two-day evaluation difficult, and therefore makes any comparisons of the treatment effect at the end of the study to earlier treatment effects problematic.

In addition, it is likely that the number of assessments over the 30 day study period were insufficient to adequately establish whether or not the treatment difference was constant over time.

For these reasons, then, we do not believe that the fundamental requirement of no significant treatment by time interaction, that is necessary to support the use of the average treatment effect over the entire duration of the trial to represent the treatment difference at the end of the trial, has been met.

In addition, although we acknowledge that your use of the MMRM followed a pre-specified plan, it is also true that this plan was adopted after the data and the results of the protocol-specified analyses were known, raising further questions about the interpretation of the results of the MMRM analyses.

For all of these reasons, then, we have concluded that the MMRM analyses cannot be considered to be more appropriate than those performed originally, and according to the protocol. Therefore, we again conclude that you have not demonstrated a robust finding on a subjective measure of sleep maintenance, and that you have not provided substantial evidence of effectiveness for Silenor as an effective treatment for patients with insomnia characterized by difficulty staying asleep.

Finally, we do not find the analyses of the IVRS measured subjective Total Sleep Time in Study 503 persuasive (i.e., a substantial number of patients did not have baseline values, and there was a significant [$p=0.03$] difference at baseline between the 6 mg group and the placebo group) or particularly relevant to the primary question of whether or not Study 501 documents a robust effect of the 6 mg group on subjective WASO.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENT

For the reasons described below, a REMS will be required as part of your approval.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Silenor (doxepin hydrochloride), if it is approved, to ensure that the benefits of the drug outweigh the potential risks of severe anaphylactic reactions and of complex sleep-related behaviors, such as sleep-driving and sleep-eating, that are associated with the class of sedative-hypnotic drugs. In addition, we have determined that a REMS is necessary for Silenor (doxepin hydrochloride) to mitigate the potential risk of suicidal thoughts and behavior in children, adolescents, and young adults, a risk associated with the class of antidepressant medications, of which Silenor (doxepin hydrochloride) is also a member. The REMS, once approved, will create enforceable obligations.

We have reviewed your proposed REMS submitted on November 11, 2008, and amended on November 21, 2008. We find that the proposed REMS is inadequate to ensure that the benefits of Silenor (doxepin hydrochloride) outweigh the risks. You must submit a revised proposed REMS prior to final approval of this new drug application.

Your revised proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Silenor (doxepin hydrochloride) tablets pose a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Silenor (doxepin hydrochloride). FDA has determined that Silenor (doxepin hydrochloride) is a product for which patient labeling could prevent serious adverse effects and has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Silenor (doxepin).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Silenor (doxepin hydrochloride).

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, by 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting

interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

The REMS assessment plan should include but may not be limited to:

- a. An evaluation of patients' understanding of the serious risks of Silenor (doxepin hydrochloride)
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Submit a revised proposed REMS that incorporates revisions as described in the paragraphs above. Specifically, your proposed REMS must include a comprehensive Medication Guide that describes the potential risks of suicidality, complex sleep-related behaviors, and (b) (4)

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22036 PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)]

in structured product labeling (SPL) format as described at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Cathleen Michaloski, MPH, Senior Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22036	ORIG-1	SOMAXON PHARMACEUTICA LS INC	SILENOR (DOXEPIN HCL)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHLEEN B MICHALOSKI
12/04/2009

RUSSELL G KATZ
12/04/2009



NDA 22-036

COMPLETE RESPONSE

Somaxon Pharmaceuticals, Inc.
3721 Valley Centre Drive, Suite 500
San Diego, CA 92130

Attention: Jodi M. Parsons, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Parsons,

Please refer to your New Drug Application (NDA) dated January 31, 2008 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxepin HCl (Silenor) 1, 3, and 6 mg Tablets.

We acknowledge receipt of your amendments dated March 6, 2008, April 10, 2008, May 1 and 30, 2008, July 24 and 31, 2008, August 11 and 29, 2008, October 9 and 23, 2008, November 7, 10, 17, and 20, 2008, and December 15, 2008.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Effectiveness

As you know, in order for a hypnotic drug product to be approved, its effect on both objective and subjective measures of particular sleep difficulties (e.g., latency, maintenance) must be established. Further, it is expected that any treatment for patients with chronic insomnia will be shown to be effective not only at the beginning of treatment, but also that its effects will persist out in time (at least for one month). In this regard, we have the following observations about the studies in your application.

We have considered the data in support of a claim for doxepin's effect on sleep maintenance. We have found no consistent effect of doxepin, at any dose, on measures of sleep latency, especially beyond Night 1.

With regard to sleep maintenance, we acknowledge the largely consistent positive findings (on both objective and subjective measures) on Night 1 across studies. However, as noted above, we expect that a similarly consistent effect will persist out in time for an effective treatment for chronic insomnia.

There appears to be evidence that doxepin 6 mg nightly has a beneficial effect on an objective measure of sleep maintenance (Waketime After Sleep Onset; WASO) prior to (at Night 15) and up to one month (at Night 29) in non-elderly adults (Study 501). However, no beneficial effect of that dose was seen on subjective WASO in that same study at Nights 15 and 29. It is true that statistically significant effects at that dose were seen on Nights 16 and Nights 30, and on the average of Nights 15 and 16 and Nights 29 and 30. Further, we note the significant findings on subjective WASO in elderly patients out to 2 months in Study 509. However, it is not immediately obvious that the effects seen at 6 mg in the elderly can be used to support a beneficial subjective effect at that same dose in non-elderly patients. For example, although we do not have complete data on this point, the likely higher plasma levels at that dose in the elderly could be driving the subjective response in these patients, and/or there may be an increased sensitivity to the effect of a given dose in the elderly compared to the non-elderly population. In any event, although the results, taken as a whole, do suggest that a 6 mg nightly dose has effectiveness, they are not robust.

Further, we note the clear statistical significance of the findings on objective WASO at 3 mg nightly out to 3 months in elderly patients in Study 503, and out to one month in non-elderly adults (Study 501). However, in Study 501, there are no statistically significant findings on subjective WASO after Night 1. In addition, there is not a robust effect on subjective WASO (nominal significance is reached on Nights 85 and 29, but not at other times, including Night 1) in Study 503. Again, although the data are suggestive, the expected clear findings on both objective and subjective measures (especially within a single study) are not found.

Finally, we note no consistent findings on either objective or subjective measures of sleep maintenance at the 1 mg dose (subjective WASO is not even significant at Night 1 in Study 503).

For these reasons, then, we have not concluded that doxepin is effective as a treatment for patients with insomnia [REDACTED] (b) (4) We are, of course, open to an argument as to why the concerns raised above should be withdrawn.

Safety

We note that no adverse reactions seen in your database would preclude approval. However, we believe that the data do raise the possibility that doxepin may prolong the QT interval, perhaps to a clinically meaningful degree.

Specifically, the data from various studies suggest a consistent prolongation in QT interval that varies from about 5 msec in studies in which drug was compared to placebo to about 10 msec in studies that compared post-treatment to pre-treatment. Where multiple doses were evaluated, there is also a suggestion of dose response. What is of particular concern is that EKGs in these

studies were not timed to dosing, (that is, EKGs were not obtained at T_{max}), and some of these changes were seen long after drug ingestion (up to several days). The explanation for these changes, especially their occurrences long after drug administration, are obscure, but could perhaps be related to levels of the nordoxepin metabolite (T_{1/2} of greater than 30 hours), some other metabolite, some other cause, or they could, of course, not be related to treatment at all. In any event, the consistent finding of QT prolongation, often well beyond T_{max}, and the apparent dose relatedness, are of concern.

We recognize, of course, that doxepin has been marketed for many years at much higher doses, with a relatively benign marketing history with regard to fatal cardiac arrhythmias. However, it is known that doxepin is associated with the occurrence of torsades de pointes, and we are not aware of any systematically collected data on the effects of doxepin, at any dose, on the QT interval. We are also aware, of course, that we had commented on a Thorough QT protocol that you had submitted on May 6, 2008. However, you have not submitted data from that study as part of an argument that the signal is dismissable.

In order to further investigate the potential for doxepin to prolong the QT interval, it may be necessary for you to conduct an *in vitro* hERG assay on doxepin and nordoxepin, a major circulating metabolite in humans. This study should be conducted in a hERG-expressing mammalian cell line under steady state conditions. Both doxepin and nordoxepin should be tested over a full concentration range. The assay should include both negative and positive controls; the positive control should be tested at a concentration near its IC₅₀.

Until and unless our concerns about doxepin's capacity to significantly prolong the QT interval can be adequately addressed, we cannot approve it for this indication.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Cathleen Michaloski, BSN, MPH, Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
2/25/2009 11:09:43 AM