

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022036Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

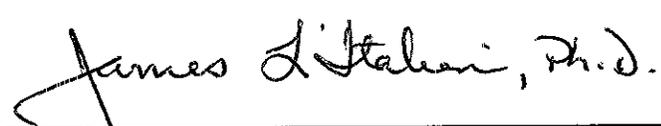
1.3.5.2. Patent Certifications

Paragraph I Certification:

Per 21 CFR 314.50 (i), Somaxon certifies, in its opinion and to the best of its knowledge, that patent information on the following referenced products has not been submitted to FDA:

Established name: doxepin HCl

NDA No.	Proprietary name, strength(s)	Sponsor:
016798	Sinequan® (doxepin HCl) Capsules 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Pfizer, Inc.
017516	Sinequan® (doxepin HCl) Oral Concentrate 10 mg/mL	Pfizer, Inc.
020126	Zonalon® (doxepin HCl) Cream, 5%	Bradley Pharms

 12 December 2007

James L'Italiani, Ph.D. Date
Sr. Vice President Regulatory Affairs & Quality Assurance

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 04/30/10 See OMB Statement on Page 3.	
		NDA NUMBER 22-026	
		NAME OF APPLICANT/NDA HOLDER Somaxon Pharmaceuticals, Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) Silenor			
ACTIVE INGREDIENT(S) Doxepin hydrochloride		STRENGTH(S) 1 mg, 3 mg and 6 mg	
DOSAGE FORM Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 5,502,047 C1		b. Issue Date of Patent 03/26/1996	
		c. Expiration Date of Patent 03/22/2013	
d. Name of Patent Owner ProCom One		Address (of Patent Owner) 3950 West Fm 967	
		City/State Buda, TX	
		ZIP Code 78610	
		FAX Number (if available) (970) 871-1655	
		Telephone Number (512) 970-4571	
		E-Mail Address (if available) fcobb@sprynet.com	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	
		Telephone Number	
		FAX Number (if available)	
		E-Mail Address (if available)	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)? Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No	
4.2 Claim Number (as listed in the patent) 8	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p>
	<p>2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4) (b) (4) and up to 6 mg, if clinically indicated. (b) (4)</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in improving (b) (4) sleep maintenance, and (b) (4) in 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 transient (N=565) insomnia.</p>

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No	
4.2 Claim Number (as listed in the patent) 11	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p>
	<p>2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4) (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated. (b) (4)</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in improving (b) (4) sleep maintenance, (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>

4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4) and up to 6 mg, if clinically indicated. (b) (4)</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4) sleep maintenance (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	

4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated.</p> <p>(b) (4)</p>	
		<p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (U-620 Treatment of Insomnia)
4.2 Claim Number (as listed in the patent) 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4) and up to 6 mg, if clinically indicated.</p> <p>(b) (4)</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4) 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>

4. Method of Use	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 15	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4).</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4).</p> <p>2.2 Dosing in the Elderly (b) (4)g, and up to 6 mg, if clinically indicated.</p> <p>(b) (4)</p>
	<p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>

4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated.</p> <p>(b) (4)</p>	
		<p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	

4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 17	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	1 INDICATION AND USAGE [REDACTED] (b) (4)	
		2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is [REDACTED] (b) (4) [REDACTED]	
		2.2 Dosing in the Elderly [REDACTED] (b) (4), and up to 6 mg, if clinically indicated. [REDACTED] (b) (4)	
		11 DESCRIPTION Silenor (doxepin HCl) is available in 1 mg, 3 mg and 6 mg strength tablets for oral administration.	
		14 CLINICAL STUDIES Silenor's efficacy in [REDACTED] (b) (4), sleep maintenance, and the [REDACTED] (b) (4) was [REDACTED] (b) (4) in 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 transient (N=565) insomnia.	

4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated.</p> <p>(b) (4)</p>	
		<p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	

4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4) a.</p> <p>2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated.</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	
4. Method of Use			
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated.</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	(U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No
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4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No
21					

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	1 INDICATION AND USAGE [REDACTED] (b) (4).
	2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is [REDACTED] (b) (4). [REDACTED] (b) (4), and up to 6 mg, if clinically indicated.
	11 DESCRIPTION Silenor (doxepin HCl) is available in [REDACTED] (b) (4) 3 mg and 6 mg strength tablets for oral administration.
	14 CLINICAL STUDIES Silenor's efficacy in [REDACTED] (b) (4), sleep maintenance, and the [REDACTED] (b) (4) was [REDACTED] (b) (4) in 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 transient (N=565) insomnia.

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	(U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No
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4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/>	Yes	<input type="checkbox"/>	No
22					

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	1 INDICATION AND USAGE [REDACTED] (b) (4).
	2 DOSING AND ADMINISTRATION 2.1 Dosing in Adults The recommended starting dose of Silenor for adults is [REDACTED] (b) (4). [REDACTED]
	2.2 Dosing in the Elderly [REDACTED] (b) (4), and up to 6 mg, if clinically indicated.
	11 DESCRIPTION Silenor (doxepin HCl) is available in [REDACTED] (b) (4), 3 mg and 6 mg strength tablets for oral administration.
	14 CLINICAL STUDIES Silenor's efficacy in [REDACTED] (b) (4), sleep maintenance, and the [REDACTED] (b) (4) was [REDACTED] (b) (4) in 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 transient (N=565) insomnia.

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia) Yes No

4.2 Claim Number (as listed in the patent) 23 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

1 INDICATION AND USAGE
 (b) (4)

2 DOSING AND ADMINISTRATION
2.1 Dosing in Adults
 The recommended starting dose of Silenor for adults is (b) (4)

2.2 Dosing in the Elderly
 (b) (4), and up to 6 mg, if clinically indicated.

11 DESCRIPTION
 Silenor (doxepin HCl) is available in (b) (4) 3 mg and 6 mg strength tablets for oral administration.

14 CLINICAL STUDIES
 Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia) Yes No

4.2 Claim Number (as listed in the patent) 24 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

1 INDICATION AND USAGE
 (b) (4)a.

2 DOSING AND ADMINISTRATION
2.1 Dosing in Adults
 The recommended starting dose of Silenor for adults is (b) (4)

2.2 Dosing in the Elderly
 (b) (4), and up to 6 mg, if clinically indicated.

(b) (4)

11 DESCRIPTION
 Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.

14 CLINICAL STUDIES
 Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.

4. Method of Use			
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>			
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? (U-620 Treatment of Insomnia)	<input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No
4.2	Claim Number (as listed in the patent) 25	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<p>1 INDICATION AND USAGE (b) (4)</p> <p>2 DOSING AND ADMINISTRATION</p> <p>2.1 Dosing in Adults The recommended starting dose of Silenor for adults is (b) (4)</p> <p>2.2 Dosing in the Elderly (b) (4), and up to 6 mg, if clinically indicated. (b) (4)</p> <p>11 DESCRIPTION Silenor (doxepin HCl) is available in (b) (4), 3 mg and 6 mg strength tablets for oral administration.</p> <p>14 CLINICAL STUDIES Silenor's efficacy in (b) (4), sleep maintenance, and the (b) (4) was (b) (4) in 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 transient (N=565) insomnia.</p>	
5. No Relevant Patents			
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.			<input type="checkbox"/> Yes

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>18 December 2007</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name James L. Italien, Ph.D.</p>	
<p>Address 3721 Valley Centre Drive, Suite 500</p>	<p>City/State San Diego, CA</p>
<p>ZIP Code 92130</p>	<p>Telephone Number (858) 480-0400</p>
<p>FAX Number (if available) 858-509-1589</p>	<p>E-mail Address (if available) jitalien@somaxon.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number</i></p>	

1.3.5.3. Statements of Claimed Exclusivity and Associated Certifications

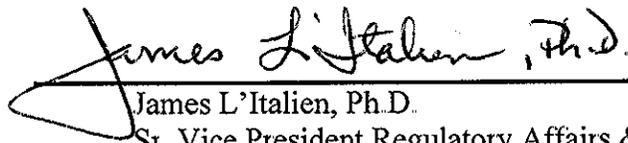
Somaxon Pharmaceuticals is claiming exclusivity for Silenor™ (doxepin HCl).

Somaxon claims exclusivity under §314.108(b)(4), the Silenor application contains new clinical investigations that are essential to approval of the application and were conducted or sponsored by the applicant.

Somaxon certifies that to the best of their knowledge each of the clinical investigations included in the application meets the definition of new clinical investigation set forth in §314.108(a).

A list of all published studies or publicly available reports of clinical investigations known to Somaxon that are relevant to the conditions for which the applicant is seeking approval, is provided in the application. Somaxon certifies that the applicant has thoroughly searched the scientific literature and, to the best of their knowledge, the list is complete and accurate and, in Somaxon's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Somaxon is seeking approval without reference to the new clinical investigation(s) in the application. The published studies or reports are insufficient as they were not adequate, well-controlled safety and efficacy studies utilizing low doses of doxepin HCl for the treatment of insomnia.

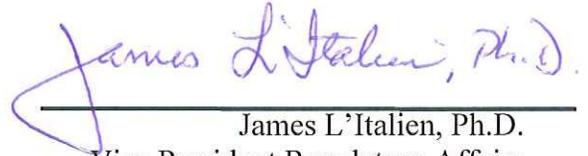
Somaxon is the sponsor named in the Form FDA-1571 for the investigational new drug application (IND 67,162) under which the new clinical investigations that are essential to the approval of its application were conducted.


James L'Italian, Ph.D.
Sr. Vice President Regulatory Affairs & Quality Assurance

12 December 2007
Date

1.3.3. Debarment Certification

Somaxon hereby certifies under FD&C Act, Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred, under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



James L'Italien, Ph.D.
Vice President Regulatory Affairs
& Quality Assurance

Sent to Sponsor 2/3/10 4pm

Brian, we have the following feedback re: your 11/11/08 REMS Proposal. If you have any questions, please contact me.

Thanks,
Cathy

Feedback from DRISK:

See the appended SILENOR (doxepin) REMS proposal for track changes corresponding to comments in this review.

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of Silenor.

b. We have some editorial comments for the Medication Guide distribution plan in this section of the proposed REMS.

c. We remind you of the required statement alerting the dispenser to provide the Medication Guide with the product to the patient. The statement must be on the carton and container of all strengths and formulations. We recommend the following language:

Unit of use:

“Dispense the enclosed Medication Guide to each patient.”

Not Unit of Use:

(b) (4)

d. We acknowledge you have included a Communication Plan with this REMS however, a Communication Plan is not necessary for the approval of this REMS.

e. Your proposed timetable for submission of assessments 18 months, 3 years, and 7 years is acceptable.

We have some editorial comments in this section of the proposed REMS.

f. Please submit for review a detailed plan to evaluate patients’ understanding about the safe use of SILENOR (doxepin). Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded “REMS Correspondence.” If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients’ understanding about the safe use of SILENOR (doxepin). This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)

- The expected number of patients to be surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Attached is a redline version of the REMS.



REMS Proposal to
Spon 2.3.10.d...

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at cathleen.michaloski@fda.hhs.gov.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22036

ORIG-1

SOMAXON
PHARMACEUTICA
LS INC

SILENOR (DOXEPIN HCL)

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/s/

CATHLEEN B MICHALOSKI

02/04/2010



NDA 022036

ACKNOWLEDGE CLASS 1 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,

We acknowledge receipt on January 21, 2010 of your January 21, 2010 resubmission to your new drug application for Silenor (doxepin HCl) 1, 3, and 6 mg tablets in the treatment of insomnia.

We consider this a complete, class 1 response to our December 4, 2009 action letter. Therefore, the user fee goal date is March 21, 2010.

If you have any questions, call me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
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)

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/s/

CATHLEEN B MICHALOSKI

02/01/2010

1/5/10 CMC requested to send the sponsor the following

Brian,

Please address the following CMC comments:

1. Please submit the analytical method and validation report for the solubility determination.
2. A reduced reporting category for the changes proposed under your comparability protocol is not feasible. As such, we recommend that you submit these changes post-approval in the form of a **Prior Approval supplement**.

Call me if any questions. Thanks,

Cathleen Michaloski, BSN / MPH
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22036

ORIG-1

SOMAXON
PHARMACEUTICA
LS INC

SILENOR (DOXEPIN HCL)

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/s/

CATHLEEN B MICHALOSKI

01/05/2010

Please refer to your December 9, 2009 letter requesting a Type A end of review conference for Doxepin in the treatment of insomnia.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting to be a Type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Jan. 20, 2010

Time: 1-2 pm EST

**Location: FDA White Oak Campus
10903 New Hampshire Ave., Silver Spring, MD
Building 22, Rm. 1315**

Current Planned CDER participants:

Robert Temple, M.D., Office Director ODE 1
Russell Katz, M.D., Neurology Division Director
Ronald Farkas, M.D. Ph.D., Clinical Team Leader
Tristan Massie, Ph.D. Biostatistician
Kun Jin, Ph.D., Supervisory Biostatistician
Martha Heimann, Ph.D., Pharmaceutical Lead, ONDQA
Sherita McLamore, Ph.D., Chemist Reviewer
Angela Men, Ph.D., Supervisory Clinical Pharmacologist
Others- TBD - OSE
Cathleen Michaloski, MPH, Sr. Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Email your final attendee list to me at least 2 days prior to your meeting so that I can give the security staff time to prepare temporary badges in advance. Foreign visitors must be cleared as well. That process needs 2 full weeks. Please notify me asap if you plan to have foreign visitors. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the meeting room: 301-796-1160; the division secretary, 301-796-2250.

Provide your background information for this meeting (three archival copies for the IND file and 12 desk copies) at least one month prior to the meeting. **If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by January 6, 2010 we may cancel or reschedule the meeting. Please submit a WORD version of the meeting questions for discussion when you submit your meeting package.**

We ask that you send the meeting questions by email to the Regulatory Project Manager at the time of submission of the briefing package. This aids the review team in what to expect when the package arrives. Send all copies of your meeting background package and any future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

Official Copies:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Desk Copies:

Cathleen Michaloski, BSN, MPH
Food and Drug Administration
White Oak CDER Building #22 Room 4342

10903 New Hampshire Avenue
Silver Spring, MD 20993

If you have questions, email or call me at **(301) 796-1123**.

Sincerely,
Cathleen Michaloski

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

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/s/

CATHLEEN B MICHALOSKI

12/17/2009

Mtg grant details



NDA #22036

MEETING DENIED

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Silenor (doxepin HCl) 1, 3, and 6 mg tablets in the treatment of insomnia.

We also refer to your September 28, 2009, correspondence requesting a meeting to discuss labeling of Silenor. We are denying the meeting because your request is premature. Our resources are focused on the NDA review and a meeting at this time would, in our view, not be an appropriate use of our resources.

If the Division believes a meeting is necessary, we will contact you for an informal teleconference.

If you have any questions, call the Regulatory Project Manager, Cathleen Michaloski, MPH 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 and Research

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

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/s/

CATHLEEN B MICHALOSKI
10/16/2009
MR denied

RUSSELL G KATZ
10/16/2009



NDA # 22036

ACKNOWLEDGE CLASS 2 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 30, 2008, received, January 31, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Silenor (doxepin HCl) 1, 3, and 6 mg tablets in the treatment of insomnia.

We also refer to your June 4, 2009 resubmission, received on June 4, 2009, that responds to our February 25, 2009 action letter.

We consider your June 4, 2009 resubmission to be a Class 2, complete response to our February 25, 2009 letter. Therefore, the user fee goal date is December 4, 2009.

If you have any question, call me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Senior Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

Cathleen Michaloski
6/16/2009 01:30:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA # 22036

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) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for doxepin HCl (Silenor).

We also refer to the April 6, 2009 meeting between representatives of your firm and the FDA. The purpose of the meeting was to discuss the end of review of NDA 22036 for doxepin in the treatment of insomnia.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathleen Michaloski, MPH 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 and Research

Enclosure - Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Meeting Type: Type B Meeting
Meeting Category: End of Review Conference
Meeting Date and Time: April 6, 2009
Meeting Location: WO 22, Room 1309
Application Number: NDA 22-036
Product Name: Silenor; Doxepin HCl
Sponsor Name: Somaxon Pharma., Inc.
Meeting Requestor: Jodi Parsons, Ph.D.
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Cathleen Michaloski, MPH

Attendees:

FDA:

Russell Katz, M.D.	Director, Division of Neurology (DNP)
Ellis Unger, M.D.	Deputy Director, ODE 1
Ron Farkas, M.D., Ph.D.	Team Leader Clinical
June Cai, M.D.	Clinical Reviewer
Kun Jin, Ph.D.	Biostatistics Team Leader
Tristan Massie, Ph.D.	Biostatistics Reviewer
Cathleen Michaloski, MPH	Regulatory Health Project Manager

Sponsor Attendees

Brian Dorsey, M.S.	Vice President, Product Development
 (b) (4)	Clinical Consultant
James L'Italien, Ph.D.	Senior Vice President, Regulatory Affairs and Quality Assurance
 (b) (4)	Regulatory Consultant

Elizabeth Ludington, Ph.D.

Senior Director, Biostatistics

(b) (4)

Clinical Consultant

Jodi Parsons, Ph.D.

Senior Director, Regulatory Affairs

Richard Pascoe

Chief Executive Officer

(b) (4)

Clinical Consultant

Regulatory Consultant

1.0 BACKGROUND

This meeting was arranged to address the sponsor's concerns for possibility of future approval of Silenor after the CR letter was issued. The main focus of the meeting was on Question#3 in their request. A summary of discussion and agreements from the meeting is presented below.

2.0 DISCUSSION

Sponsor Questions for the NDA 22-036 End-of-Review Meeting

1. The Thorough QT Study, SP-D0801, is fully compliant with applicable guidances for the evaluation of QT prolongation, neither doxepin dose (6 mg and 50 mg) showed any increase in QT interval, and the positive control (moxifloxacin) results were within historical ranges (around 8 to 10 ms). Therefore, this study should serve as a definitive evaluation, obviating the need for a hERG evaluation.

Somaxon proposes that the data from the Thorough QT clinical study of doxepin (SP-D0801) serve as the basis of assessment for the risk of QT prolongation, and that a hERG study, as described by the Division in the Complete Response letter, will therefore not be necessary. Does the Division agree?

FDA Preliminary Response:

Yes, we agree that if the Thorough QT study is adequate, a hERG study does not need to be conducted.

Meeting Discussion: None

2. SP-D0801 is a unique study with limited comparability to the integrated safety analysis sets in the NDA. Only two of the four groups (doxepin 6 mg and placebo) are relevant to Silenor safety, and any integration would be limited to the All Subjects safety analysis set. Based on a review of the safety results of SP-D0801, the results of new integrated analyses would not alter the overall safety conclusions already presented. The Division indicated in the Complete Response letter that there were no adverse reactions seen in our database that would preclude approval.

(b) (4)



FDA Preliminary Response:

No. The Thorough QT study report must be submitted to the NDA as part of your complete response to the FDA Complete Response letter. It is, however, acceptable to present in your complete response the safety data from the QT study separately from data from other studies.

Meeting Discussion: None

3. We note the Division's emphasis on subjective WASO (sWASO) in its comments on subjective support for sleep maintenance. In the NDA for Silenor and in our response below to the stated deficiencies, however, we discuss subjective sleep maintenance in terms of subjective Total Sleep Time (sTST) as the primary support parameter. This emphasis is consistent with the Division's agreement in our End-of-Phase 2 Meeting (See minutes dated May 25, 2005, Appendix 7) and with each of our pivotal studies, in which sTST was identified prospectively in Phase 3 as the key subjective sleep maintenance parameter in the sleep laboratory studies (SP-0501, SP-0503), and the primary variable in the outpatient study (SP-0509). In addition, sWASO when measured in the sleep laboratory setting correlates poorly with objective WASO (Kryger et al., 1991). Subjective efficacy is best assayed in the home setting using evaluations afforded by the interactive voice response system (IVRS)(Krystal et al., 2003). Further, the IVRS approach, which allows for an integrated evaluation over multiple nights, provides critical support to the overall evaluation of subjective sleep maintenance.

The Division has raised a concern regarding the durability of efficacy in sleep maintenance insomnia as measured by subjective parameters in both adult and elderly patients, and cites some specific findings in terms of subjective WASO (sWASO). Somaxon believes that using subjective Total Sleep Time (sTST) as agreed with the Division during the End-of-Phase 2 Meeting, along with self-rated Clinical Global Impression (CGI) scores, is appropriate to support an

assessment of durable sleep maintenance as measured subjectively in elderly and non-elderly adult patients. Does the Division agree?

FDA Preliminary Response:

You can base your argument for efficacy on sTST, but the acceptability of your argument remains a matter for review. We note that you designated sTST results collected *at the sleeping center* as a primary subjective endpoint, not sTST data collected *by IVRS*. From review of your NDA, our conclusions based on the sTST results collected at the sleeping center were similar to our conclusions based on sWASO; neither endpoint allowed us to conclude that doxepin was effective. Interpretability of sTST data collected by IVRS is considerably weakened by the fact that this data was not originally designated a primary endpoint, such that analysis post-hoc lacks statistical soundness. Also, we note that the sTST data collected by IVRS appears to lack data from a large number of subjects (49/240) with missing baseline scores for many (31 patients).

We do not consider CGI to be a valid measure of sleep maintenance, but will nevertheless consider your argument about how it might support efficacy.

Meeting Discussion:

The sponsor presented the efficacy data on “sleep maintenance” using IVRS collected sTST and proposed that the IVRS data are acceptable efficacy parameters that show convincing sustained effects. The sponsor suggested that the efficacy data for Silenor was as strong as efficacy data that supported approval of precedent drugs.

The statistics reviewers discussed problems with missing data and imputation for the IVRS data. The Division indicated that the primary subjective endpoint remained a central issue in the evaluation of efficacy, while Dr. Katz indicated that the Division would also consider the strength and consistency of the whole package of data. Dr. Katz stressed that convincing evidence of efficacy in the non-elderly population was necessary for approval.

No agreement was reached about the acceptability of the sponsor’s efficacy data, which remains an issue for review of their complete response.

- 4. In light of the favorable QT results and efficacy information on sleep maintenance contained in this document and in the NDA, combined with prior agreements with the Division on efficacy endpoints (See Pre-NDA Meeting minutes dated June 28, 2006; End-of-Phase 2 Meeting Minutes dated May 25, 2005; and the FDA Response to the Request for Type A Meeting dated September 1, 2006; Appendix 7) and regulatory precedents for previously approved insomnia agents, Somaxon maintains that there is sufficient evidence for approval of Silenor to treat insomnia. The issue of durability with respect to subjective efficacy is therefore a labeling issue rather than an approvability issue. Does the Division agree?*

FDA Preliminary Response:

No. You can make these arguments in your complete response, but their acceptability will be a matter for review. As stated in the CR letter, we find the issue of durability of efficacy to be an approvability issue.

Meeting Discussion: None

5. Somaxon proposes to resubmit revised labeling consistent with demonstrated efficacy of Silenor for sleep maintenance and [REDACTED] (b) (4) [REDACTED] in elderly and non-elderly adults, in addition to a safety update/summary of the Thorough QT study as a complete response to the Division's action letter dated February 25, 2009.

Does the Division concur that a resubmission comprised of a revised label and summary of the Thorough QT safety study, may adequately address the deficiencies as noted in the Complete Response letter?

FDA Preliminary Response:

No. Submission of revised labeling and a safety update with only a summary of the Thorough QT study would not be considered a complete response to the FDA Complete Response letter. The adequacy of your response to the FDA Complete Response letter remains a matter of review.

Meeting Discussion: None

6. *In accordance with guidance (Classifying Resubmissions in Response to Action Letters, April 1998), Somaxon believes the inclusion of the proposed safety update and revised label would be consistent with and constitute a Class 1 resubmission, with a 2-month review cycle. Does the Division agree?*

FDA Preliminary Response:

No. Since the resubmission will include new study data it does not constitute a Class 1 resubmission.

Meeting Discussion: None

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/s/

Russell Katz

5/4/2009 02:09:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-036

Somaxon Pharmaceuticals, Inc.
Attention: James L'Italien, Ph. D
Sr. VP, Regulatory Affairs & Quality Assurance
3721 Valley Centre Drive, Suite 500
San Diego, CA 92130

Dear Dr. L'Italien:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Silenor (Doxepin HCl) Tablets dated January 30, 2008.

We also refer to your amendments dated October 9, 2008 November 17, 2008, containing a comparability protocol in support of the proposed changes:

1. The addition of a colored, (b) (4) film-coating as a means to visually distinguish between different strengths and assure uniform distribution of color which includes the following

(b) (4)

2. (b) (4)

The proposed reporting category for the changes included in the comparability protocol is a CBE Supplement.

We have reviewed the referenced material and have the following comments and recommendations.

1. These changes could potentially have an adverse effect on tablet erosion and dissolution. Moreover, it has been determined that Doxepin can not be classified as a BCS Class I drug product for the following reasons:

Solubility Assessment:

- i. (b) (4)
- ii.

2. A reduced reporting category for these changes is not feasible. As such, we recommend that you submit these changes post-approval in the form of a **Prior Approval supplement**.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
2/25/2009 02:42:57 PM



PDUFA GOAL DATE EXTENSION

NDA #22-036

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) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxepin HCl (Silenor), 1, 3 and 6 mg Tablets.

On November 21, 2009, we received your information amendment dated November 20, 2008. The receipt date of the amendment is within 3 months of the primary user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended primary user fee goal date is **February 28, 2009**.

If you have any questions, call Cathleen Michaloski, 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 and Research

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/s/

Russell Katz
12/4/2008 03:27:16 PM



NDA 22-036

INFORMATION REQUEST LETTER

Somaxon Pharmaceuticals, Inc.
Attention: Jodi M. Parsons, Ph.D.
Senior Director, Regulatory Affairs
3721 Valley Centre Drive, Suite 500
San Diego, CA 92130

Dear Dr. Parsons:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxepin HCl (Silenor).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please be advised that changes to the drug product manufacturing process including but not limited to the inclusion of a (b) (4) step should be reported to the agency under the appropriate filing category.
2. You indicate that the basis for manufacturing tablets with average hardness values of (b) (4) Kp were:

- (b) (4)
- (b) (4)

You further indicate that the tablets will have a (b) (4) that is spread further apart on the surface of the tablet. Indicate if the film coated tablets used in the above studies had a (b) (4) that is spread further apart on the surface of the tablet.

3. Include a test and an acceptance criterion for the microbial limits in the drug product specification or justification for the exclusion as per ICH Q6A.

4. The acceptance criterion for the unidentified impurities should be based on the maximum daily dose and not the potency. As such, we recommend that you provide a single, uniform acceptance criterion for the individual unidentified impurities for the 1 mg, 3 mg and 6 mg drug product based on the maximum daily dose as per ICHQ3B (R)
5. The test method and acceptance criterion that you proposed for the identification of the drug substance in the drug product is not specific. Adopt a method that is specific for the drug substance or include a second chromatographic procedure that is based on a different separation method as outlined in ICH Q6A
6. The strength of the drug product is expressed as Doxepin; however, Doxepin HCl is listed on the label as an established name. Revise the label so that the established name corresponds to the strength.
7. Update the post-approval stability commitment to include storage under accelerated conditions for the first three commercial batches.
8. The results of the multi-media dissolution study were greater than (b) (4) in 15 minutes for all samples tested. As such, we recommend that you revise the dissolution specification to $Q = (b) (4)$ in 15 minutes to be more reflective of the data and consistent with BCS Class 1 compounds.
9. (b) (4)
10. The limit that you propose for the total impurity is excessively broad and not reflective of the data. Revise the acceptance criteria for the total impurity to be more reflective of the data.
11. In the stability section of your application, you indicate that photostability studies were performed on the exposed drug product. ICH Q1B indicates the following:

...the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light...

As such, we request that you provide additional photostability data to demonstrate that the primary and or secondary packaging provides adequate protection for the drug product when exposed to light.
12. (b) (4) for the manufacture of Doxepin HCl is deficient. The DMF holder has been notified of this by separate letter which includes a list of the deficiencies.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
9/29/2008 10:28:18 AM



FILING COMMUNICATION

NDA 22-036

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

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

Dear Ms. Parsons,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxepin HCl (Silenor).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **December 1, 2008**.

We also acknowledge receipt of submissions dated March 6, 2008 and April 10, 2008.

We request that you submit the following information:

Clinical Comments:

1. For special searches on suicidality, please categorize suicidal cases using the Columbia suicidal analysis scale.
2. For common Adverse Event (AE) tables, please provide a table for events that occurred, in placebo controlled trials, at a rate of 5 percent or more and for which the rate was at least twice that of placebo.
3. For less common AEs, please provide a table for events that occurred at rates less than or equal to 1%.

4. For the demographic analysis of AEs, please analyze each common, drug-related adverse event incidence for each demographic variable by calculating the odds ratios of the event in each subgroup as well as the common odds ratio for event across subgroups followed by the use of Breslow-Day Chi-Square test to test for homogeneity of the odds ratios across the subgroups, with determination of the p-value for this test.
5. For the demographic analysis of efficacy, please provide the p-values for cross treatment group comparisons.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We are granting you a waiver for pediatric studies up to age 6 and we will defer studies for children ages 6 through 16 years.

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 and Research

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/s/

Eric Bastings
4/14/2008 04:01:19 PM
Signed for Dr. Katz.