October 20, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned, on behalf of Somaxon Pharmaceuticals, Inc. ("Somaxon"), submits this petition under section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 C.F.R. § 355(j)) and 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs take special consideration in the review of any abbreviated new drug application ("ANDA") for a generic version of SILENOR® (doxepin) and to withhold approval of any such application until the conditions set forth below in this petition are satisfied. Somaxon holds the new drug application ("NDA") for SILENOR.

I. Actions Requested

Somaxon respectfully requests the Food and Drug Administration ("FDA") to take the following actions:

1. Decline to grant any ANDA for a generic doxepin product listing SILENOR as the Reference Listed Drug ("RLD") if the ANDA relies on a Biopharmaceutics Classification System (BCS)-biowaiver in lieu of establishing in vivo bioequivalence to SILENOR.

2. Require that ANDA applicants for generic versions of SILENOR conduct two in vivo bioequivalence studies and:
   a. That the studies be conducted under both fasted and fed conditions; and
   b. That in addition to employing FDA’s standard bioequivalence testing requirements—i.e., the ratio of plasma doxepin peak drug concentration ("C_max") and area under the concentration curve ("AUC") for the generic formulation to the C_max and AUC for SILENOR have 90% confidence intervals within the range of 80 to 125%—FDA also require the partial AUC truncated at such time point(s) as FDA may deem appropriate to meet the bioequivalence standard of 90% confidence intervals within the range of 80 to 125%.
II. Brief Statement of Grounds

ANDA applicants must demonstrate, among other things, that the proposed generic drug is bioequivalent to the RLD.\(^1\) To do this, the applicant typically must submit either (a) data from in vivo bioequivalence testing, or (b) information sufficient to permit FDA to waive the submission of in vivo bioequivalence evidence.\(^2\) According to FDA’s Biopharmaceutics Classification System Guidance, biowaivers may be available for certain rapidly dissolving Class I—i.e., highly soluble and highly permeable—immediate release (“IR”) drug products.\(^3\)

FDA should decline to grant a BCS-biowaiver for any ANDA for a generic doxepin product listing SILENOR as the RLD. According to a published absolute bioavailability study, the mean absolute bioavailability of doxepin is only 29%.\(^4\) Other data have demonstrated that food increases the bioavailability of SILENOR and that the dose-normalized plasma exposures for SILENOR 6 mg were lower than those for Sinequan\(^{®}\) (doxepin) 50 mg.\(^5\) Taken together, these data suggest that absorption of SILENOR may vary based on dose (i.e., that the pharmacokinetics may be nonlinear) and whether SILENOR is taken under fed or fasted conditions.

Given these particular circumstances, different formulations of doxepin may exhibit different rates and extents of absorption in vivo. BCS classification therefore may not be a good predictor of bioequivalence of an ANDA formulation. Under the BCS system, a generic formulation of doxepin that has different activity from SILENOR—and is not bioequivalent to SILENOR—could potentially be granted a biowaiver. Accordingly, Somaxon requests that FDA not permit biowaivers for ANDAs listing SILENOR as the RLD.

Instead, FDA should require that such ANDA applicants establish in vivo bioequivalence to SILENOR 6 mg. Because SILENOR is associated with a significant food effect, FDA should require such studies in both the fed and fasted states. This will help ensure that any generic doxepin product is therapeutically equivalent to the RLD. To ensure that

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\(^2\) Id.

\(^3\) FDA, Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System 2 (Aug. 2000) [hereinafter BCS Guidance].


\(^5\) Synopsis, A Randomized, open-label, study to assess the effect of food on the PK of doxepin HCL (n=16) [hereinafter Synopsis Study SP-D0504] (Exhibit 2); Synopsis, A Randomized, open-label study to assess the relative bioavailability of Silenor\(^{TM}\) (doxepin HCl) 6 mg tablets compared to Sinequan\(^{®}\) (doxepin HCl) 50 mg capsules (n=24) [hereinafter Synopsis Study SP-D0507] (Exhibit 3). Sinequan\(^{®}\) is a registered mark of Warner-Lambert Co. LLC.
patients taking approved generics do not suffer residual next day effects, these studies should also demonstrate that the partial AUC truncated at such time point(s) as FDA may deem appropriate meet the bioequivalence standard of 90% confidence intervals within the range of 80 to 125%.

III. Complete Statement of Grounds

A. Background

1. SILENOR®

FDA approved SILENOR on March 17, 2010, for the treatment of insomnia characterized by difficulty with sleep maintenance. It is supplied in IR tablets for oral administration in 3 and 6 mg strengths. The approved prescribing information (‘PI’) indicates that SILENOR “should be taken within 30 minutes of bedtime” and, “for faster onset and to minimize the potential for next day effects, [it] should not be taken within 3 hours of a meal.”

2. ANDA Filings

The first substantially complete ANDA for doxepin hydrochloride tablets listing SILENOR as the RLD was submitted on September 16, 2010.7 To the best of Somaxon’s knowledge, there are now four such ANDAs pending at FDA. Somaxon received paragraph IV notification letters from Actavis Elizabeth LLC and Mylan Pharmaceuticals Inc. dated November 2, 2010, from Par Pharmaceutical, Inc. dated December 21, 2010, and from Zydus Pharmaceuticals USA, Inc. dated May 12, 2011.

Although FDA approved SILENOR on March 17, 2010, Somaxon did not begin commercial distribution of its product until September 1, 2010. Thus, the first substantially complete ANDA was submitted to FDA a mere 15 days after SILENOR first became commercially available. Given the short time between commercial availability and the first substantially complete ANDA submission, Somaxon believes that one or more of the ANDAs likely are relying on a BCS Class I biowaiver.

3. Statutory and Regulatory Background: Bioequivalence

Under FDCA § 505(j)(2)(A)(iv), an ANDA must contain, among other things, “information to show that the new drug is bioequivalent to the listed drug.”8 FDA’s regulations provide that any person submitting an ANDA to FDA must include either “[e]vidence demonstrating that the drug product that is the subject of the abbreviated new drug application is

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6 Silenor® PI (Mar. 2010) § 2.3 and 12.3 (Exhibit 4).
bioequivalent to the reference listed drug” or “[i]nformation to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence as provided in [21 C.F.R. § 320.21(f)].”9 With respect to demonstrating bioequivalence,

[t]wo drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.10

Evidence demonstrating bioequivalence “shall be obtained using one of the approaches for determining bioavailability set forth in [21 C.F.R.] §320.24.”11 That section lists the various acceptable approaches in “descending order of accuracy, sensitivity, and reproducibility,” starting with in vivo testing.12

In certain circumstances, FDA waives the requirement for in vivo bioequivalence testing. One of those circumstances is the BCS waiver. The BCS Guidance provides that “BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances” so long as the RLD is also rapidly dissolving and the test product exhibits similar dissolution profiles to the RLD.13 Sponsors requesting biowaivers for ANDAs based on the BCS should, among other things, submit data supporting high solubility, high permeability, and rapid and similar dissolution.14

B. Argument

1. Doxepin Hydrochloride Formulations Are Not Suitable for BCS Biowaiver

For several reasons, doxepin is not suitable for a BCS-biowaiver. First, FDA’s BCS Guidance appears to reflect the assumption that a drug with high permeability likely has high bioavailability. According to FDA’s BCS Guidance,

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9 21 C.F.R. § 320.21(b).
10 Id. at § 320.23(b).
11 Id. at § 320.21(e).
12 Id. at § 320.24(b)(1)(i).
13 BCS Guidance, supra note 3, at 10. The BCS Guidance describes when a drug substance is highly permeable, highly soluble, and rapidly dissolving. See id. at 2-3.
14 Id. at 10-12
In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.\textsuperscript{15}

Thus, high permeability, in conjunction with high solubility and rapid dissolution, can be used as a predictor for absorption. This assumption, however, does not appear to hold for doxepin. To Somaxon's knowledge the only absolute bioavailability study of doxepin to date failed to conclusively demonstrate that it is highly bioavailable.\textsuperscript{16} To the contrary, that study found that "the mean absolute oral bioavailability was 29% for both doxepin isomers."\textsuperscript{17} This is well below the 90% absolute bioavailability that the BCS Guidance identifies as one of the ways drug permeability may be determined.

This low bioavailability is indicative of a significant level of complexity of doxepin \textit{in vivo}, which confounds the apparent assumption underlying the BCS waiver. It is not known to what extent the incomplete oral bioavailability of doxepin is due to incomplete absorption versus extensive intestinal metabolism, in addition to substantial first pass hepatic extraction, and/or other factors. This is because, to Somaxon's knowledge, a human mass balance study of radiolabeled doxepin hydrochloride has not been performed.

Second, doxepin's observed food effect further suggests that BCS Class I classification may not be a good predictor of doxepin bioequivalence. Food appears to increase the bioavailability of doxepin compared to the fasted state. This suggests that the extent of oral absorption may be considerably less than 90% in the recommended fasted dosing state. In Study SP-D0504 (the "Food Effect Study"), administration of the 6 mg tablet after a high-fat meal resulted in a delayed rate and increased extent of absorption relative to fasted state dosing.\textsuperscript{18} In the fed state, the plasma median time to peak concentrations ($T_{\text{max}}$) was delayed by approximately three hours, the plasma doxepin $C_{\text{max}}$ was approximately 15% higher, and the plasma doxepin AUC$_{0-\infty}$ was approximately 41% higher. Taken together, these data suggest that doxepin may not be highly bioavailable and, therefore, not appropriate for a biowaiver.

\textsuperscript{15} \textit{Id.}

\textsuperscript{16} Yan, \textit{supra} 4, 615-623. In this randomized, two-treatment, two-period, two-sequence crossover design pharmacokinetic study, 12 healthy male volunteers were given single doses of commercial doxepin intravenously and orally on two occasions separated by a washout period. \textit{Id.} In the study the oral dose was "85.5 mg doxepin hydrochloride (equivalent to 75 mg free base containing 12.0 mg Z-doxepin + 63.0 mg E-doxepin, Apo-doxepin\textsuperscript{TM}, Apotex, Inc., Weston, Ontario, Canada)." \textit{Id.} at 617. The study appears to have been done in a fasted state. \textit{Id.}

\textsuperscript{17} \textit{Id.} at 619.

\textsuperscript{18} Synopsis Study SP-D0504, \textit{supra} note 5.
Finally, available dose-normalized exposure data also suggest that BCS Class I classification may not be a good predictor of doxepin bioequivalence. Study SP-D0507 showed that dose-normalized plasma doxepin exposures—\(C_{\text{max}}/\text{dose}\) and \(\text{AUC}/\text{dose}\)—in the fasted state for the SILENOR 6 mg tablet were approximately 27-36% lower than dose-normalized exposures for the marketed SINEQUAN (doxepin) 50 mg capsule. The non-bioequivalence of the dose-normalized plasma doxepin exposures between the two products might be explained by incomplete oral absorption from the SILENOR tablet formulation. The observed nonlinearity between SILENOR and SINEQUAN could also be due to saturation of the metabolism processes at higher doses.

Accordingly, the available data suggest a significant level of complexity with respect to doxepin absorption. This complexity precludes use of the BCS Class I factors (high solubility, high permeability and rapid dissolution) as a predictor for bioequivalence. Thus, Somaxon requests that FDA decline to grant a BCS-biowaiver to any ANDA applicant for a generic doxepin product listing SILENOR as the RLD. This is consistent with FDA’s draft guidances on doxepin hydrochloride capsules (August 2010) and tablets (September 2010) (“Draft Doxepin Guidances”), one, if not both of which, predate the ANDA submitted on September 16, 2010, and any subsequent ANDAs. Neither draft guidance mentions the possibility of a BCS-biowaiver.

2. Doxepin ANDAs should be required to conduct fasted and fed in vivo bioequivalence studies

In lieu of a biowaiver, FDA should require that generic formulations of doxepin conduct in vivo bioequivalence studies under fasted conditions—the recommended dosing

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19 See Synopsis Study SP-D0507, supra note 5. Peak plasma concentrations (\(C_{\text{max}}\)) of SILENOR increased in an approximately dose-proportional manner for 3 and 6 mg doses and the AUC for the 3 and 6 mg doses demonstrated dose proportionality. Synopsis, Phase I, Pharmacokinetic Study of doxepin HCL in Healthy Volunteers (Study SP-0405) designed to: (1) characterize the PK profile of doxepin 1 mg, 3 mg, and 6 mg capsules in terms of dose proportionality, and (2) assess the bioequivalence of the 6 mg tablets and 6 mg capsules in healthy, adult male volunteers [hereinafter Synopsis Study SP-0405] (Exhibit 5).


21 In contrast, FDA specifically noted in its guidance on emtricitabine there are “2 Options: BCS or In-Vivo Studies.” FDA, Guidance on Emtricitabine (rev. Aug. 2010). The guidance goes on to discuss the “BCS Waiver option” and notes that “[i]t may be possible to request a waiver of in-vivo testing for all the strengths of this product provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the [BCS Guidance] is submitted in the application.” Id.; see also FDA, Guidance on Granisetron Hydrochloride (rev. Aug. 2010). In addition, there are a number of draft guidance documents, which reference a BCS waiver option. See, e.g., FDA, Draft Guidance on Ramelteon (Mar. 2009); FDA, Draft Guidance on Levetiracetam (Apr. 2009).
condition for SILENOR—and fed conditions. Requiring a fasted study is consistent with FDA’s general recommendations for bioequivalence studies for IR tablets.\textsuperscript{22} Requiring a food effect study is consistent with FDA’s Draft Doxepin Guidances, which recommend fasting and fed studies.\textsuperscript{23} As noted above, a substantial food effect has been observed with SILENOR.\textsuperscript{24} Information about this effect is included in the approved labeling, including a statement that SILENOR should not be taken within three hours of a meal “for faster onset and to minimize the potential for next day effects.”\textsuperscript{25} To ensure that any generic doxepin product will be therapeutically equivalent to the RLD, FDA should require ANDA applicants to demonstrate equivalence under fed conditions.

3. Doxepin ANDAs should be required to demonstrate equivalence at specific time points

In addition to FDA’s traditional bioequivalence parameters of $C_{\text{max}}$ and AUC, FDA should also require ANDA applicants to demonstrate equivalence to SILENOR at specific time points. This can be demonstrated by showing that the partial AUC, truncated at such time point(s) as FDA may deem appropriate, meets the bioequivalence standard of 90% confidence intervals within the range of 80 to 125%. This will help ensure that generic versions of SILENOR will be therapeutically equivalent to the RLD.\textsuperscript{26}

\textsuperscript{22} See FDA, Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations 12 (Mar. 2003) [hereinafter BA & BE Guidance].

\textsuperscript{23} Draft Doxepin Hydrochloride Tablet Guidance, supra note 20; Draft Doxepin Hydrochloride Capsule Guidance, supra note 20.

\textsuperscript{24} See Synopsis Study SP-D0504, supra note 5.

\textsuperscript{25} PI, supra note 6, § 12.3.

\textsuperscript{26} FDA has itself noted that for orally-administered immediate-release drug products, it “recommends use of partial AUC as an early exposure measure” in the setting where “[a]n early exposure measure may be informative on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive).” BA & BE Guidance, supra note 22, at 8-9. FDA recommends “that the partial area be truncated at the population median $T_{\text{max}}$ values for the reference formulation” and “that at least two quantifiable samples be collected before the expected peak time to allow adequate estimation of the partial area.” Id. Similarly, FDA has required BE showings of partial AUC in the context of another sleep aid, Ambien CR\textsuperscript{®} (zolpidem tartrate extended-release tablets). Ambien CR\textsuperscript{®} is a registered mark of Sanofi Societe Anonyme. There FDA agreed that “the evaluation of a generic zolpidem ER product based solely upon traditional FDA bioequivalence criteria will not ensure therapeutic equivalence between the generic product and Ambien CR, and that therapeutic equivalence to Ambien CR should be demonstrated as a function of time using additional criteria for the fasting studies.” FDA Response to Citizen Petition of sanofi-aventis, Docket No. FDA-2007-P-0182 at 12 (Oct. 13, 2010).

(continued...)
Somaxon believes that this additional step is necessary for two, related reasons. First, Study SP-D0506 suggests a relationship between the doxepin plasma concentrations and time-course and the clinical effect time-course (e.g., the onset and offset of pharmacodynamic effects). This relationship appears to play an important role in determining whether patients will experience next-day residual effects.

In this study, the largest effect on psychomotor function—changes consistent with sedation—occurred approximately three hours after dose administration. This is a time point near the estimated median $T_{\text{max}}$ (3.5) for plasma concentrations of doxepin, following administration of doxepin with or without sertraline. Mean DSST, SCT, and VAS scores appeared to return approximately to baseline at 6–8 hours following administration of doxepin with or without sertraline. This temporal correlation between the most significant effect on psychomotor function and $T_{\text{max}}$ suggests a relationship between plasma concentrations and PD effects relevant to sleep. Doxepin appears to produce a sedative-like effect on psychomotor performance and subjective experience that takes effect shortly after dosing. This effect then typically resolves in 6 to 8 hours. Figure 1, below, presents a representative example of a mean doxepin plasma concentration curve, which shows that the concentration of doxepin was maintained above approximately 0.6 ng/mL until approximately 8 hours. This effect was also...
observed by an FDA reviewer during FDA’s review of the SILENOR NDA. According to this reviewer, a “residual PD effect was detected until doxepin blood levels decreased to about 0.6 ng/ml, at 8 hours post-dose.”

**Figure 1: Mean Doxepin and Nordoxepin Plasma Concentration (ng/mL) Over Time**

Second, a food effect is observed when SILENOR is taken in a fed state. The $T_{\text{max}}$ of doxepin occurred 3.5 hours after oral administration of a 6 mg dose to fasted healthy subjects. In the Food Effect Study, the plasma $T_{\text{max}}$ in the fed state was delayed by approximately 3 additional hours, the plasma doxepin $C_{\text{max}}$ was approximately 15% higher, and the plasma doxepin $\text{AUC}_{0-\infty}$ was approximately 41% higher. Thus it appears that food alters the rate and extent of absorption of SILENOR. Further, the extent of absorption for SILENOR may be considerably less than complete, particularly for the recommended fasted state dosing condition.

Seen in the context of a temporal correlation between psychomotor function and $T_{\text{max}}$, the doxepin food effect is quite significant. Studies in adults and the elderly collectively suggest that with SILENOR residual pharmacodynamic effects upon awakening are modest to

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30 FDA, Drug Approval Package (NDA 22036), Medical Review, Cross Discipline Team Leader Review by Ronald Farkas, MD, PhD, at 3 [hereinafter Drug Approval Package (NDA 22036)].

31 Synopsis Study SP-0405, supra note 19; Figure 3 Study SP-0405 (Exhibit 7).

32 PI, supra note 6, § 12.3.

33 Synopsis Study SP-D0504, supra note 5.
negligible, and are more likely to occur with the higher 6 mg dose.\textsuperscript{34} These studies utilized DSST, SCT, and VAS assessments, following nighttime administration of SILENOR (fasted state dosing), and assessed next-day psychomotor function within 1 hour of awakening (approximately 8 to 10 hours post-dose). If SILENOR is administered at nighttime with food, however, the residual morning concentrations of doxepin in plasma after a nighttime sedating dose may be much higher due to the increase in $C_{\text{max}}$ and AUC. Similarly, these effects may last beyond the point that the patient wakes-up due to the significant delay in $T_{\text{max}}$. Combined, this could cause both the frequency and intensity of residual effects upon awakening to be significantly enhanced following fed state dosing.

This could pose significant safety risks for patients. Indeed, FDA recently has expressed concern about the possible risks associated with next-day impairment with hypnotic medications.\textsuperscript{35} Similarly, during the SILENOR NDA review, FDA reviewers expressed concern regarding the observed food effect. For example, the Clinical Pharmacology/Biopharmaceutics section of a Cross Discipline Team Leader (CDTL) Review for SILENOR discusses the concern that “changes in AUC and $T_{\text{max}}$” when SILENOR is administered in the fed state “could affect the onset and maintenance of drug effect, and increase the likelihood of next day residual effects.”\textsuperscript{36} The CDTL review points out that the “large delay in $T_{\text{max}}$, from 3-4 hours post-dose in fasted state to 6-8 hours post-dose in fed state . . . . is of concern because $T_{\text{max}}$ in the fed state essentially coincides with wake time, suggesting increased risk of next-day residual drug effects.”\textsuperscript{37} The review indicates that “[t]his concern is strengthened by Study SP-0506, which . . . included pharmacodynamic assessments of doxepin throughout the day after morning dose in

\textsuperscript{34} In a one-night, double-blind study (Study 502) conducted in 565 healthy adult subjects experiencing transient insomnia, SILENOR 6 mg showed modest negative changes in SCT and VAS within 1 hour of awakening. See Synopsis, A Phase III, Randomized, Double Blind, Placebo Controlled, Parallel-Group, Multicenter Study to Assess the Efficacy and Safety of Doxepin HCl (6 mg) for the Treatment of Transient Insomnia in Adult Subjects ($N=565$) (Exhibit 8). In a 35-day, double-blind, placebo-controlled, parallel group study (Study 501) of SILENOR 3 and 6 mg in 221 adults with chronic insomnia, small decreases in the DSST and SCT occurred in the 6 mg group within 1 hour of awakening. See Synopsis, A Phase III, Randomized, Double Blind, Placebo Controlled, Parallel-Group, Multicenter Study to Assess the Efficacy and Safety of Doxepin HCl (3 mg and 6 mg) in Primary Insomnia Patients with Sleep Maintenance Difficulties ($N=229$) (Exhibit 9). In a 3-month, double-blind, placebo-controlled, parallel group study (Study 503) in 240 elderly subjects with chronic insomnia, SILENOR 1 mg and 3 mg was comparable to placebo on DSST, SCT, and VAS. Synopsis, A Phase III, Randomized, Double Blind, Placebo Controlled, Parallel-Group, Multicenter Study to Assess the Long Term Efficacy and Safety of Doxepin HCl (1 mg and 3 mg) in Primary Elderly Insomnia Patients with Sleep Maintenance Difficulties ($N=240$) (Exhibit 10).

\textsuperscript{35} See, e.g., Letter from Russell Katz, Director, Division of Neurology Products, Office of Drug Evaluation 1, Center for Drug Evaluation and Research, to Brian Dorsey, Somaxon Pharmaceuticals, Inc. (Aug. 8, 2011) [hereinafter Information Request] (Exhibit 11).

\textsuperscript{36} Drug Approval Package (NDA 22036), supra note 30, at 3.

\textsuperscript{37} Id.
the fasted state . . .”38 The review goes on to state that “[t]he maximum PD effect of Silenor was strongly correlated with doxepin Tmax at 3 hours, and residual PD effect was detected until doxepin blood levels decreased to about 0.6 ng/ml, at 8 hours post-dose.”39 In addition, it states that “[i]n fed state in study 0504, doxepin blood level did not decrease to 0.6 ng/ml until about 10 hours after dosing.”40

As a result, FDA required the PI to indicate that SILENOR “[s]hould not be taken within 3 hours of a meal” in order “[t]o minimize the potential for next day effects” and “for faster onset.”41 Accordingly Somaxon requests that FDA require that pharmacokinetic equivalence between a generic formulation and SILENOR be demonstrated by showing that the partial AUC truncated at such time point(s) as FDA may deem appropriate meet the bioequivalence standard of 90% confidence intervals within the range of 80 to 125%. This will provide greater assurance of equivalence between generics and SILENOR in terms of expected therapeutic effects. Somaxon proposes that FDA require that the partial AUC truncated at AUC$_{6-12}$ and the population T$_{max}$ value for the RLD—i.e., AUC$_{0-3.5}$ and AUC$_{3.5-4}$—or other time point(s) that FDA may deem appropriate meet the bioequivalence standard.42

IV. Conclusion

As demonstrated above, several factors confound the ability to use BCS Class I as a predictor for bioequivalence. Doxepin appears to have low (29%) absolute bioavailability and, unexpectedly, demonstrates a significant food effect. Thus, Somaxon believes it is not appropriate to waive in vivo bioequivalence testing for generic doxepin formulations based on SILENOR as the RLD. Instead, to ensure clinical equivalency to SILENOR, Somaxon requests FDA require any ANDA applicant listing SILENOR as the RLD to establish in vivo bioequivalence to SILENOR under fasted and fed conditions. Somaxon also requests that any such applicants be required to demonstrate that the partial AUC truncated at such time point(s) as FDA may deem appropriate, as well as the traditional bioequivalence parameters C$_{max}$ and AUC, meet the bioequivalence standard of 90% confidence intervals within the range of 80 to 125%.

38 Id. (emphasis omitted).
39 Id.
40 Id.
41 See PI, supra note 6, §§ 2.3 and 12.3.
42 Information Request, supra note 35. Somaxon’s proposal that FDA require the partial AUC truncated at AUC$_{6-12}$ is based on FDA’s statement in its Information Request that it is “particularly interested in effects . . . on the range of hourly blood levels between 6 and 12 hours after dosing.” Id. An integrated exposure as measured by AUC$_{6-12}$ would show comparable drug amounts to assure equal safety.
V. Required Material

A. Environmental Impact

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

B. Economic Impact

An economic impact statement will be submitted at the Commissioner’s request.

VI. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: October 18, 2010—when Somaxon became aware, based on information on the FDA website, of the date on which the first substantially complete ANDA containing a “Paragraph IV” patent certification listing SILENOR as the RLD was submitted to FDA—and the ensuing several weeks—during which Somaxon collected information regarding the likely timing of such application. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am an employee and officer of Somaxon Pharmaceuticals, Inc., and am making these representations on behalf of the company as part of my responsibilities as an employee and officer. I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

[Signature]
Brian T. Norsey
Senior Vice President, Technical Operations
Somaxon Pharmaceuticals, Inc.