

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022036Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Biopharmaceutics Review

NDA: 22-036
Sequence No: 0019
Submission Date: June 4, 2009
Type of Submission: Resubmission following Complete Response 3S
Product name: Silenor™ (doxepin HCl)
Dosage Form: Tablet
Dosage Strengths: 1 mg, 3 mg, and 6 mg
Sponsor: Somaxon Pharmaceuticals, Inc.

Background

Silenor (doxepin HCl) is indicated for the treatment of insomnia. It is an immediate release tablet available in three strengths (1 mg, 3 mg, and 6 mg). The tablet formulation was developed using standard (b) (4)

(b) (4)

(b) (4) the comparability protocol described the sponsor intent to make some changes to the drug product. The sponsor is planning to add a colored, (b) (4) film-coat as a mean to visually distinguish between different strengths. However, in order to make this addition, the sponsor has to perform other changes to the manufacturing process, including the following:

(b) (4)

According to the CMC reviewer, Dr. Sherita McLamore, the above proposed changes are considered Level 2 according to SUPAC IR and require Prior Approval Supplement.

Assessing Solubility

The solubility of doxepin hydrochloride was determined in a non-GLP manner. The aqueous solubility of doxepin hydrochloride was tested at pHs of 1.0, 6.8, and 7.4 using the shake-flask method. Triplicate samples were prepared for each buffer system and at equilibration, and the pH was verified using a calibrated pH meter. The sponsor reported that the thermodynamic pKa values for doxepin and its metabolite desmethyl doxepin are 8.96 and 9.75, respectively, at 25 °C.

The highest dose strength of doxepin hydrochloride is 6 mg. When dissolved in 250 mL it yields 0.024 mg/mL. To establish that aqueous solubility exceeds the criteria for designation as highly soluble (0.024 mg/mL), solubility samples were prepared at a target concentration of about 1 mg/mL.

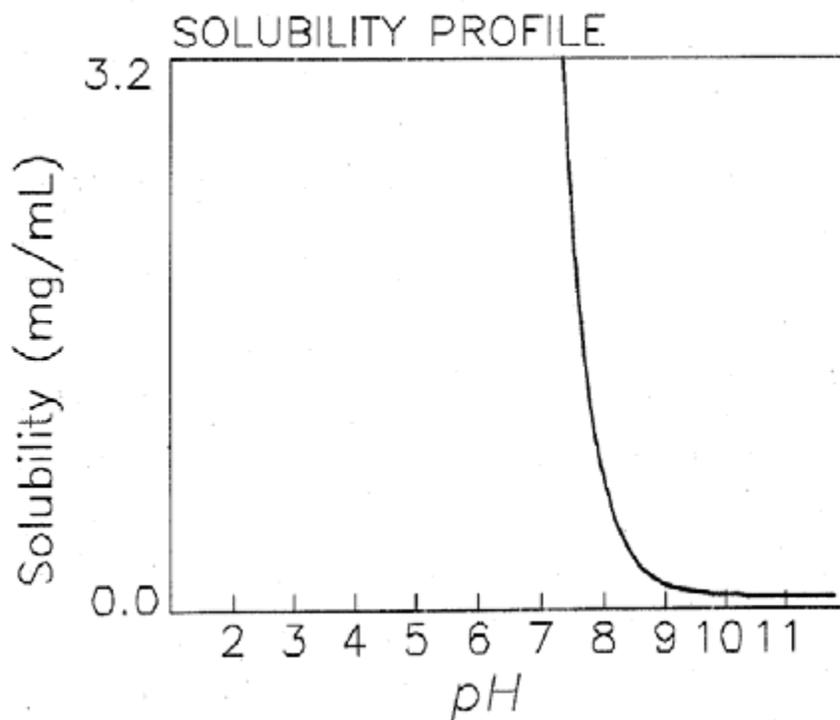
The sponsor stated that all samples appeared to be clear solutions (no solids were visible), indicating that the actual solubility of doxepin hydrochloride is greater than 1 mg/mL. The sponsor attributed the measured concentrations that were less than the initial concentration (1mg/mL) (b) (4)
The solubility results are listed in Table 1 below.

Table 1: Solubility of Doxepin Hydrochloride in Different pH Buffers (Mean, n=3)

pH	Measured Concentration (mg/mL)	Mean ± SD (mg/mL)
7.4	0.919	0.934 ± 0.0862
	1.03	
	0.856	
6.8	0.834	0.958 ± 0.108
	1.02	
	1.02	
1.0	0.935	0.971 ± 0.0466
	1.02	
	0.954	

In the comparability protocol, the sponsor provided the following information using the potentiometrically-generated solubility data shown in Figure 1 and Table 2 below.

Figure 1: Solubility Profile for Doxepin



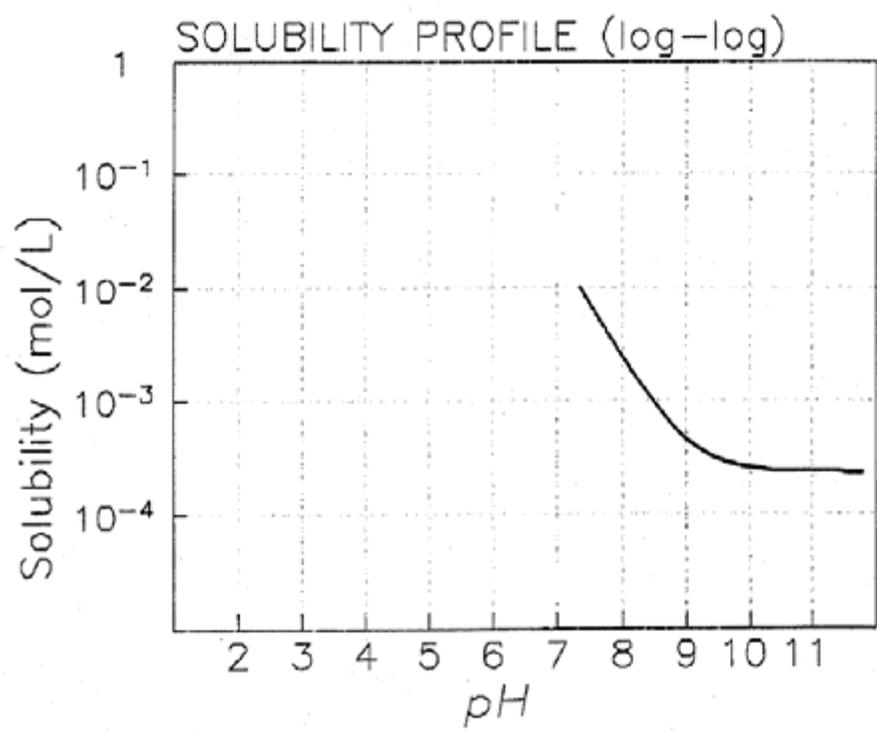


Table 2: Solubility Profile Data for Doxepin

pH	S (µg/mL)	Dose Limit Profile (mg)	pH	S (µg/mL)	Dose Limit Profile (mg)
7.5	2596.00	649	9.7	91.62	23
7.6	2075.00	519	9.8	88.29	22
7.7	1662.00	415	9.9	85.76	21
7.8	1334.00	334	10.0	83.67	21
7.9	1074.00	269	10.1	82.06	21
8.0	867.80	217	10.2	80.73	20
8.1	704.10	176	10.3	79.75	20
8.2	574.40	144	10.4	78.90	20
8.3	476.30	119	10.5	78.29	20
8.4	397.00	99	10.6	77.75	19
8.5	328.20	82	10.7	77.37	19
8.6	277.80	69	10.8	77.03	19
8.7	234.80	59	10.9	76.79	19
8.8	202.70	51	11.0	76.57	19
8.9	176.10	44	11.1	76.42	19
9.0	155.60	39	11.2	76.29	19
9.1	139.00	35	11.3	76.19	19
9.2	126.00	31	11.4	76.10	19
9.3	115.60	29	11.5	76.05	19
9.4	107.30	27	11.6	75.99	19
9.5	100.90	25	11.7	75.96	19
9.6	95.64	24	11.8	75.92	19
			11.9	75.90	19

Reviewer's Note:

The sponsor stated in the comparability protocol submitted in January 30, 2008 that the intrinsic solubility of doxepin HCl was determined potentiometrically using a (b) (4) titration methodology. All experiments were titrated from low to high pH, and precipitate was observed. The sponsor also reported that the observed solubility ranged from 649 mg/250 mL at pH=7.5 to 19 mg/250 mL at pH=11.9, and concluded that according to Henderson-Hasselbach theory, doxepin HCl clearly demonstrates solubility values consistent with a Class 1 molecule as defined in the Biopharmaceutical Classification System (BCS).

In response to Information Request correspondence dated November 24, 2009, the sponsor submitted additional information on solubility. The information submitted comprised of six pages final report generated by (b) (4). The report included a description of the analytical method (not a full report) used for the determination of the measured concentrations. And, it was noted that the solubility determination was made using a shake-flask method.

Overall, the solubility information submitted is conditionally acceptable. The sponsor will be asked to submit the analytical method and validation report.

Additionally, the sponsor will be asked to clarify which method is used to determine doxepin solubility (i.e. potentiometric or shake-flask).

Comments to Chemistry Reviewer

The CMC reviewer asked that a review be conducted to determine whether doxepin HCl qualifies as a highly soluble and highly permeable drug according to the Biopharmaceutics Classification System.

For the permeability determination, refer to review dated 11/28/2008. For the solubility determination, the additional information submitted as a result of the Information Request dated 11/24/2009 is acceptable. However, the sponsor is requested to submit the analytical method and validation report. Additionally, the sponsor is requested to report whether the solubility determination was made using the potentiometric method or the shake-flask method.

Based on the information submitted, doxepin can be classified as BCS Class 1 (HS/HP) drug pending confirmation of the BCS Committee.

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.
Biopharmaceutics Expert
Office of New Drug Quality Assessment

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22036

ORIG-1

SOMAXON
PHARMACEUTICA
LS INC

SILENOR (DOXEPIN HCL)

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

/s/

PATRICK J MARROUM

11/30/2009

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Doxepin HCl
NDA:	22-036
PRODUCT (Brand Name):	SILENOR
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	1, 3, and 6 mg
INDICATION:	Insomnia
NDA TYPE:	505(b)(2)
SUBMISSION DATES:	1/31/2008, 3/6/2008, 4/10/2008, 5/1/2008, 5/30/2008, 7/24/2008, 7/31/2008, 8/11/2008, 8/29/2008, 10/9/2008
SPONSOR:	Somaxon Pharmaceuticals, Inc.
REVIEWER:	Ju-Ping Lai, Ph.D.
ACTING TEAM LEADER:	Veneeta Tandon, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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1.0 EXECUTIVE SUMMARY

Doxepin HCl is a dibenzoxepin tricyclic agent. Oral doxepin (Sinequan[®]) was approved as an antidepressant and anxiolytic at recommended dosages of 75-150 mg/day in 1969. A topical cream 5% (Zonalon[®]) has also been approved for the treatment of short-term, moderate pruritis with atopic dermatitis or lichen simplex chronicus.

According to the sponsor, at low doses (1, 3 and 6 mg), doxepin consistently acts as a selective H1 antagonist and exhibits sleep-promoting activity without the side effects that are typically associated with higher doses of doxepin. The sponsor has therefore proposed to market doxepin HCl (SILENOR[®]) for the indication of insomnia.

Doxepin HCl (SILENOR[®]) will be marketed as 1, 3 and 6 mg tablets. The starting dose for adults and elderly patients is (b)(4)mg and (b)(4)mg once daily, respectively. Doses could be increased up to 6 mg if clinically indicated.

This 505(b)(2) application consists of five Phase I clinical pharmacology studies in 104 healthy subjects. These studies include dose proportionality (1-6 mg) with a BE study comparing 6 mg SILENOR versus 6 mg capsule, drug interaction studies with cimetidine and sertraline, food effect study with 6 mg SILENOR and relative BA study with Sinequan[®]. The clinical efficacy and safety was evaluated in six well-controlled Phase II and Phase III studies in 1423 adults, elderly patients and as well as healthy adults.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 22-036. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Phase IV requirements and the Agency's labeling recommendations.

Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review on page 29 should be conveyed to the sponsor.

In addition, the following comments should be conveyed to the sponsor and the medical officer, respectively.

Comments for the sponsor:

The following comments regarding the solubility and permeability information submitted for classification of doxepin as a BCS class I drug should be conveyed to the sponsor:

Doxepin could not be classified as BCS class I drug product as complete information was not available in this submission. If the sponsor intends to establish the classification, the sponsor should submit the following for review, in addition to the other solubility and permeability aspects submitted in the original NDA submission:

- Complete solubility information at pH 1-7.5.
- The assessment of system suitability for the permeability method based on 20 model drugs and the extent of absorption of each of these drugs.

Please refer to FDA guidance: Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System for all information necessary for solubility and permeability classification.

Comments for the medical officer:

- Cimetidine increases the exposure of doxepin by 2-fold. These exposures are greater at all time points in the plasma concentration profile. The increased exposure of doxepin following cimetidine co-administration, specifically at 6 and 8 hours are of concern for the next day residual effects of doxepin. The mean doxepin plasma concentrations were 0.70 vs 1.30 ng/mL (doxepin alone vs doxepin+cimetidine) and 0.55 vs 0.99 ng/mL (doxepin alone vs doxepin+cimetidine), respectively, at 6 and 8 hours post dosing. These increased concentrations following co-administration were even higher than the C_{max} (0.86 ng/mL) after doxepin alone. A recommendation is therefore made by limiting maximum dose of doxepin in adults and elderly to 3 mg, when doxepin is co-administered with cimetidine.
- Food increases exposure of doxepin by 41% and delays the T_{max} of doxepin by 3 hours (i.e at 6-8 hours postdose). There could be a delay in the onset of effect as well as the next day residual effects of doxepin may be significant when taken with food. Based on the dosing instructions in the Phase II and III clinical trials in which patients were instructed to take meal at least 3 hours before the drug administration, the dosing instruction in the label is recommended to be changed to: “Doxepin should not be taken within 3 hours of meal intake” in lieu of sponsor proposal of “ Do not take Doxepin with or immediately after a meal”.
The dosing instructions in relation to the meals were given particularly for the sleep laboratory assessment days and no instructions were given for the other at home days. Therefore differences in subjective and objective measures should be taken into consideration.

1.2 PHASE IV REQUIREMENTS

The following Phase IV requirements should be conveyed to the sponsor:

1. In vivo drug interaction study with a potent CYP 2C19 inhibitor should be conducted.
2. In vivo drug interaction study with a potent CYP 2D6 inhibitor should be conducted.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Dose proportionality: The pharmacokinetic parameter, C_{max}, of doxepin appears to be dose proportional within doses of 1 mg, 3 mg and 6 mg. AUC at doses of 3 mg and 6 mg demonstrated the dose proportionality while AUC for 1 mg could not be evaluated due to the limitation of the assay sensitivity. Similar results were seen with nordoxepin. Dose proportionality was not observed in the study comparing 6 mg tablet and 50 mg capsule (Sinequan) utilizing a dose-normalization comparison. Higher C_{max} and AUC were observed in the 50 mg capsule (Sinequan) to a modest extent (~30%).

Intrinsic Factors:

Age: No studies were conducted for evaluating the age effect on doxepin PK. Based on a published population pharmacokinetic study, clearance of doxepin was decreased by about one third from age 20 to age 75. Clinical studies were conducted using a lower starting dose of (b) (4) mg in elderly and will be labeled as such.

Gender: Using the pooled data from the five Phase I studies, mean C_{max} and AUC of doxepin were 16% and 8% higher in females. These differences are not likely to be clinically significant.

Race: Using the pooled data from the five Phase I studies, within ethnic groups not all races were adequately represented. There was only enough African-Americans (n=11) to permit an informal comparison to Whites (n=84). Approximately 50% higher C_{max} (1.36 vs. 0.90 ng/mL) and 18% higher AUC (18.5 vs. 15.7 ng*hr/mL) were observed in African-Americans while the distributions were overlapped between the two races. Given the high variability in PK, these differences observed are not expected to be clinically significant.

Extrinsic Factors:

Drug-drug Interactions:

Effect of doxepin on pharmacokinetics of other drugs:

- There was no change in steady-state concentrations of sertraline when co-administered with doxepin indicating doxepin has no effect on sertraline PK.

Effect of other drugs on doxepin pharmacokinetics:

- A non-specific CYP 450 inhibitor, cimetidine increases doxepin concentrations in AUC and C_{max} by approximately 2 folds. **Dose adjustment: The maximum**

dose of doxepin in adults and elderly should be 3 mg, when doxepin is co-administered with cimetidine.

- A weak CYP 2D6 inhibitor, sertraline increases doxepin concentrations. AUC_{0-t}, AUC_{0-∞}, and C_{max} of doxepin were approximately 28%, 21%, and 32% higher, respectively. PD parameters DSST, SCT, and VAS scores were similar between the two groups. In both groups, maximum effects occurred approximately 3 hours postdose and these scores returned to approximately baseline at 6–8 hours postdose. The differences in PK are not likely to be clinical relevant. No dosage adjustment is necessary.

Biopharmaceutics:

BCS Class: Based on the sponsor, doxepin has high solubility and high intrinsic permeability; however, an official agency classification could not be established at this time due to the lack of sufficient information provided for a BCS classification.

Relative Bioavailability:

- The proposed to-be-marketed formulation at 6 mg tablet is bioequivalent to the 6 mg capsule formulation used in earlier Phase I, II and III studies.
- The proposed to-be-marketed formulation of 6 mg tablet demonstrated approximately 30% lower exposure compared to the approved 50 mg Sinequan[®] based on dose normalization comparison. Mean C_{max} (derived from dose-normalized plasma concentrations) and median T_{max} were approximately 27% lower and 0.5 hour slower, respectively, following administration of doxepin 6 mg when compared with Sinequan[®] 50 mg.

Food Effect: High fat food increases AUC by 41% and C_{max} by 15% and delayed T_{max} from 3-4 hours to 6-8 hours postdose. In addition, in 5/6 clinical studies, the patients were instructed to take meals at least 1.5 hours before admitting to the clinical sleep laboratory and arrive the site at least 2 hours before bedtime, as seen in the Table below. Based on this, the dose was administered at least 3 hours after their evening meal. However, the instructions for meal time related to the drug administration were not given at the home setting. It is therefore recommended to not take Silenor within 3 hours of meal intake.

Phase II/III	Study number	Patient populations	Duration	Meal time relative to dosing	Place dose administered
II	SP-0401	Adults	2 nights	≥ 3 hours ^a	sleep laboratory ^b
	SP-0402	Elderly	2 nights	≥ 3 hours ^a	sleep laboratory ^b
III	SP-0501	Adults	35 nights	≥ 3 hours ^a	sleep laboratory ^b and self administered at home ^c
	SP-0503	Elderly	85 nights	≥ 3 hours ^a	sleep laboratory ^b and self administered at home ^c
	SP-0502	Healthy adults	1 night	≥ 2.5 hours ^a	sleep laboratory ^b
	SP-0509	Elderly	28 nights	Not indicated	self administered at

					home ^c
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^a: For doses administered at sleep laboratory.

^b: Instructions regarding meal time prior to the admission to the sleep center were provided to the patients.

^c: Guidelines for at home administration relative to meals were not provided.

Ju-Ping Lai, Ph.D.

Division of Clinical Pharmacology I _____

Acting Team Leader: Veneeta Tandon, Ph.D. _____

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

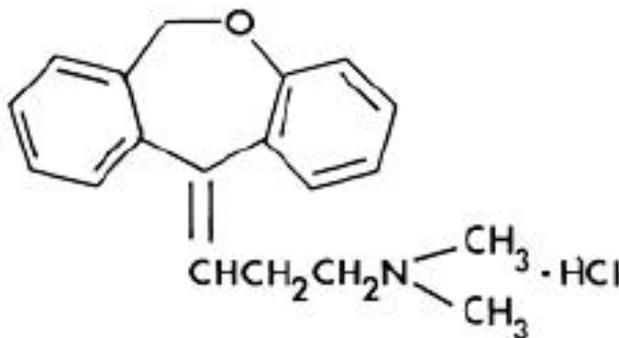
2.1.1 *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Dosage Form/Strengths: 1, 3 and 6 mg tablets

Indication: SILENOR[®] (doxepin HCl) is indicated for insomnia in patients 18 years and older.

Pharmacologic Class: Doxepin is a dibenzoxepin tricyclic agent

Chemical Name: Doxepin has the chemical name: 1-Propanamine, 3-dibenz[*b,e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-hydrochloride; *N,N*-Dimethyldibenz[*b,e*]oxepin- Δ 11(6*H*), γ -propylamine hydrochloride; 11-3(-dimethylaminopropylidene)-6,11-dihydrodibenz[*b,e*]oxepin hydrochloride. It has an empirical formula of C₁₉ H₂₁ NO•HCl and a molecular weight of 315.84.



Physical Characteristics: The drug substance is a white, crystalline powder with a slight amine-like odor. Doxepin is highly soluble and highly permeable based on the sponsor; however, it has not yet been classified as a BCS Class I drug by the agency at this time.

Formulation: Silenor Tablets (1 mg, 3 mg, and 6 mg) are (b) (4). The composition of Silenor Tablets (1 mg, 3 mg, and 6 mg) is shown in the table below:

Name of Ingredient	Reference to Standards	Function	Unit Formula (mg)		
			1 mg	3 mg	6 mg
Doxepin HCl	USP	Drug Substance	(b) (4)	3.39 ^b	6.78 ^c
(b) (4)	Components are USP/NF ^d	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate	USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide ^a	USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Yellow No. 10	D&C	Colorant	(b) (4)	(b) (4)	(b) (4)
(b) (4)	FD&C	Colorant	(b) (4)	(b) (4)	(b) (4)
Blue No. 1	FD&C	Colorant	(b) (4)	(b) (4)	(b) (4)
Total Tablet Weight			150 mg		

^a Equivalent to 1.0 mg of doxepin as the free base

^b Equivalent to 3.0 mg of doxepin as the free base

^c Equivalent to 6.0 mg of doxepin as the free base

(b) (4)

2.1.2 What is the mechanism of action and therapeutic indication?

Doxepin (SILENOR) is a sleep-promoting agent and is indicated for insomnia. According to the sponsor, doxepin binds to human histamine H₁ receptors with high affinity (<1 nM), where it functions as a selective antagonist and thereby promotes sleep initiation and maintenance. Doxepin has lesser affinity at a number of other neurotransmitter sites, but at the recommended doses for doxepin (SILENOR), these sites are not likely to contribute to the pharmacological activity. There was no detectable activity at benzodiazepine recognition sites or at other sites on the GABA receptor complex determined by doxepin administration.

2.1.3 What are the proposed dosages and route of administration?

Dosage and administration (Sponsor's Proposed):

Adults: The recommended initial dose is (b) (4) mg once daily. The daily dose can be increased to 6 mg, if clinically indicated.

Elderly: The recommended initial dose is (b) (4) mg once daily in elderly patients. The daily dose can be increased to (b) (4) mg and up to 6 mg, if clinically indicated.

SILENOR should not be taken with or immediately after a meal.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

Five Phase I clinical pharmacology studies were performed in 104 healthy subjects to evaluate dose linearity, bioequivalence, relative bioavailability, food effect and drug-drug interactions.

Six double-blind, placebo-controlled studies (2 Phase II and 4 Phase III) were conducted in 1,423 subjects with chronic or transient insomnia for supporting the efficacy of doxepin for the treatment of insomnia.

Key features of the Phase I studies are given in the following Table:

Study Number	Enrolled N (male/female)	Completed N (male/female)	Doses (Formulation)	Objectives
SP-0405	16 (16/0)	15 (15/0)	1, 3, 6 mg (capsules) 6 mg (tablet)	<ul style="list-style-type: none"> Assess PK dose proportionality of 1 mg, 3 mg, and 6 mg doxepin capsules Assess relative bioavailability of doxepin 6 mg tablets compared to 6 mg capsules
SP-0504	16 (6/10)	15 (6/9)	6 mg (tablet)	<ul style="list-style-type: none"> Assess the effect of a high fat meal on doxepin PK
SP-0505	24 (9/15)	22 (8/14)	6 mg (tablet)	<ul style="list-style-type: none"> Assess effect of cimetidine on single dose PK of doxepin
SP-0506	24 (16/8)	24 (16/8)	6 mg (tablet)	<ul style="list-style-type: none"> Assess effect of sertraline on doxepin single dose PK Assess effect of doxepin on steady-state sertraline PK Assess PD interaction of sertraline and doxepin
SP-0507	24 (19/5)	23 (18/5)	6 mg (tablet) 50 mg (capsule)	<ul style="list-style-type: none"> Assess relative bioavailability of doxepin 6 mg tablets compared to Sinequan[®] 50 mg capsules
Totals	104 (66/38)	99 (63/36)	--	--

The description of these five Phase I studies was provided in the Individual Study Review section.

Key features of the Phase II and III studies are given in the following Table:

Study, Location, and Dates	Study Design	Duration	Subject Population	Primary Efficacy Variable	Secondary Efficacy Variables	Treatment Arms & Subjects in the Efficacy Analysis
Phase 2 Chronic Insomnia – Objective PSG Studies Conducted in a Sleep Laboratory						
SP-0401 11 centers in the US 07/2004 to 09/2004	DB, R, PC, MC, 4-period crossover	2 nights on each dose, 5- or 12-day washout between periods	18–64 yrs with chronic insomnia with sleep maintenance difficulties	WTDS	WASO, TST, SE, LPS, SE Hr 8, WTAS (by PSG) & sTST, sWASO, LSO	Placebo = 66 Doxepin 1 mg = 66 Doxepin 3 mg = 66 Doxepin 6 mg = 67 Total = 67
SP-0402 11 centers in the US 09/2004 to 01/2005	DB, R, PC, MC, 4-period crossover	2 nights on each dose, 5- or 12-day washout between periods	≥65 yrs with chronic insomnia with sleep maintenance difficulties	WTDS	WASO, TST, SE, LPS, SE Hr 8, WTAS (by PSG) & sTST, sWASO, LSO	Placebo = 73 Doxepin 1 mg = 74 Doxepin 3 mg = 75 Doxepin 6 mg = 74 Total = 76
Phase 3 Chronic Insomnia – Objective PSG Studies Conducted in a Sleep Laboratory and Outpatient Setting						
SP-0501 22 centers in the US 06/2005 to 12/2005	DB, R, PC, MC, PG, fixed dose	35 nights of DB dosing	18–64 yrs with chronic insomnia with sleep maintenance difficulties	WASO	WTDS, TST, SE, LPS, SE Hr 8, WTAS, SE last quarter (by PSG) & sTST, sWASO, LSO	Placebo = 73 Doxepin 3 mg = 75 Doxepin 6 mg = 73 Total = 221
SP-0503 31 centers in the US 09/2005 to 09/2006	DB, R, PC, MC, PG, fixed dose	85 nights of DB dosing	≥65 yrs with chronic insomnia with sleep maintenance difficulties	WASO	WTDS, TST, SE, LPS, SE Hr 8, WTAS, SE last quarter (by PSG) & sTST, sWASO, LSO	Placebo = 81 Doxepin 1 mg = 77 Doxepin 3 mg = 82 Total = 240
Phase 3 Chronic Insomnia – Subjective Study Conducted in an Outpatient Setting						
SP-0509 32 centers in the US 01/2006 to 09/2006	DB, R, PC, MC, PG, fixed dose	28 nights of DB dosing	≥65 yrs with chronic insomnia with sleep maintenance difficulties	sTST	LSO and sWASO	Placebo = 124 Doxepin 6 mg = 130 Total = 254
Phase 3 Transient Insomnia – Objective PSG Study Conducted in a Sleep Laboratory						
SP-0502 6 centers in the US 02/2006 to 06/2006	DB, R, PC, MC, PG, single dose	1 night of DB dosing	Healthy adults (25–55 yrs) with transient insomnia	LPS	WASO, WTDS, TST, SE, SE Hr 8, WTAS, SE last quarter (by PSG) & sTST, sWASO, LSO	Placebo = 282 Doxepin 6 mg = 283 Total = 565
Total Subjects in the ITT Analysis Set = 1,423 (858 with chronic insomnia [including 288 adults and 570 elderly subjects] and 565 adults with transient insomnia).						

Notes: DB=Double-blind; MC=Multicenter; PC=Placebo Controlled; PG=Parallel Group; OP=Outpatient, R=Randomized. Studies [SP-0401](#) and [SP-0402](#) used a crossover study design. In [SP-0401](#), 67 subjects received at least one dose of doxepin, and in [SP-0402](#), 76 subjects received at least one dose of doxepin.

Of all 1,423 subjects, 858 subjects had chronic insomnia (288 adults and 570 elderly subjects) and 565 subjects had transient insomnia. A total of 863 subjects received doxepin (580 with chronic insomnia and 283 with transient insomnia) and 699 subjects received placebo (417 with chronic insomnia and 282 with transient insomnia).

As shown in the table, below are clinical studies that collected efficacy data. These studies were conducted in adults (patients and healthy subjects) as well as the elderly patient populations.

Five studies (SP-0401, SP-0402, SP-0501, SP-0503, and SP-0509) were conducted in subjects with chronic insomnia, while study SP-0502 was conducted in healthy subjects with transient insomnia. The chronic insomnia studies were primarily designed to evaluate the effects of doxepin on sleep maintenance improvement.

- Two Phase 2 chronic insomnia objective polysomnography (PSG) studies SP-0401 (adults) and SP-0402 (elderly) conducted in a sleep laboratory.
- Two Phase 3 chronic insomnia objective PSG studies SP-0501 (adults) and SP-0503 (elderly) conducted in a sleep laboratory and in an outpatient setting.
- One Phase 3 chronic insomnia subjective study SP-0509 (elderly) conducted in an outpatient setting.
- One Phase 3 transient insomnia objective PSG study SP-0502 (healthy adults) conducted in a sleep laboratory.

Nightly doses of 1 mg, 3 mg, or 6 mg from 1 night up to 3 months of double-blind treatment were performed to evaluate the efficacy of doxepin in both inpatient (sleep laboratory) and outpatient settings.

Five studies, SP-0401, SP-0402, SP-0501, SP-0503, and SP-0502, collected 8-hour PSG recordings (objective efficacy data) and a morning sleep questionnaire subjective data completed by subjects.

Study SP-0509 collected only subjective data using an Interactive Voice Response System (IVRS) whereas Study SP-0503 collected subjective data using both the morning questionnaire and the IVRS.

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

Description of the Objective and Subjective Efficacy Evaluations were Wake After Sleep Onset (WASO) and subjective Total Sleep Time (sTST) for sleep maintenance, Latency to Persistent Sleep (LPS) and Latency to Sleep Onset (LSO) for sleep onset, and Sleep Efficiency (SE) in Hour 8 for the prevention of early morning awakenings. The five chronic insomnia studies utilized sleep maintenance as the primary variable, and the transient study utilized a sleep onset as the primary variable. The efficacy endpoints in the various Phase II and III clinical studies are given in the following table.

Study No.	Sleep Maintenance						Sleep Onset		Prevention of Early Morning Awakenings			
	Objective (PSG)				Subjective		Objective (PSG)	Subjective	Objective (PSG)			
	WASO	WTDS	TST	SE	sTST	sWASO	LPS	LSO	SE Hr 8	WTAS	SE Last Qtr	
Phase 2 Chronic Insomnia Studies												
0401	X	X ¹	X	X	X	X	X	X	X	X	X	ND
0402 ²	X	X ¹	X	X	X	X	X	X	X	X	X	ND
Phase 3 Chronic Insomnia Studies												
0501	X ¹	X	X	X	X	X	X	X	X	X	X	X
0503 ²	X ¹	X	X	X	X	X	X	X	X	X	X	X
0509 ²	NA	NA	NA	NA	X ¹	X	NA	X	NA	NA	NA	NA
Phase 3 Transient Insomnia Study												
0502	X	X	X	X	X	X	X ¹	X	X	X	X	X

¹ Primary efficacy variable for the study.

² Study performed in the elderly (defined in protocol as ≥65 years of age).

Notes: X=variable assessed during corresponding clinical study; NA=Not applicable; ND=Not done; WASO=Wake After Sleep Onset; WTDS=Wake Time During Sleep; TST=Total Sleep Time; SE=Sleep Efficiency; sTST=subjective TST; sWASO=subjective WASO; LPS=Latency to Persistent Sleep; LSO=Latency to Sleep Onset; SE Hr 8=SE in Hour 8; WTAS=Wake Time After Sleep; and SE Last Qtr=SE in the last quarter of the night.

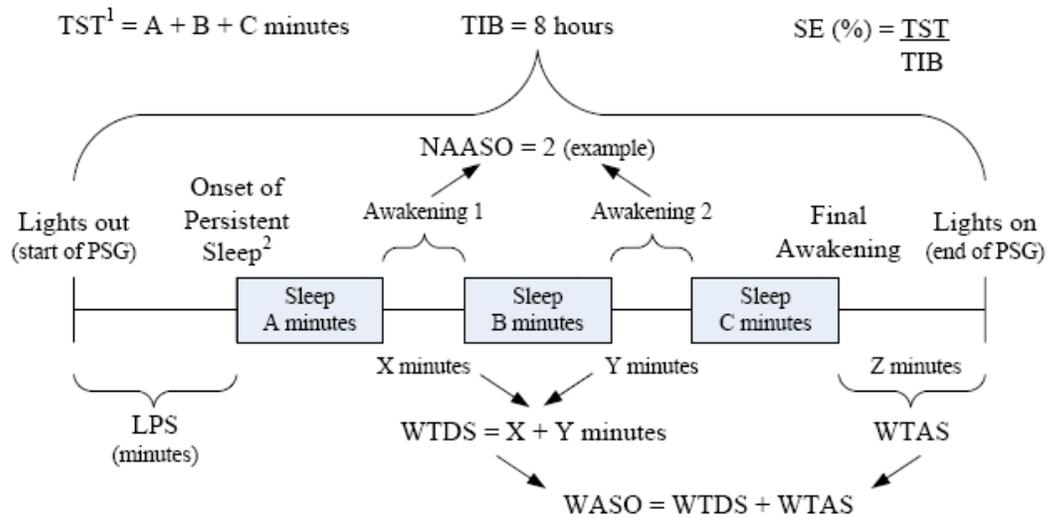
Primary support variables identified for each claim are shaded, while the secondary support variables are not shaded.

All efficacy variables are defined in [Section 2.7.3.1.3](#), Description of the Objective and Subjective Efficacy Evaluations.

Subjective efficacy variables were obtained using the morning questionnaire completed in the sleep laboratory for all studies, except for the outpatient study [SP-0509](#) that obtained subjective efficacy data using the IVRS. [Study SP-0503](#) also collected subjective data using the IVRS.

- **WTDS**-Amount of time awake after the onset of persistent sleep and prior to the final awakening, or end of the 8-hour PSG recording.
- **WTAS**-Amount of time awake after the final awakening until the end of the 8-hour PSG recording.
- **Wake After Sleep Onset (WASO)**-Amount of wake time after the onset of persistent sleep to the end of the 8-hour PSG recording; calculated as the sum of WTDS and WTAS.
- **Subjective Total Sleep Time (sTST)**- Amount of sleep time from lights out to the end of the 8-hour PSG recording.
- **Latency to Persistent Sleep (LPS)**-Minutes from lights out to the first 10 minutes of consecutive sleep.
- **Latency to Sleep Onset (LSO)**
- **Sleep Efficiency (SE)**-Calculated as TST divided by the total time spent in bed (480 minutes) multiplied by 100.

The following is a schematic of the various efficacy endpoints during the study.



¹ = Also includes all sleep time prior to the onset of persistent sleep
² = Onset of first sleep episode of ≥ 10 consecutive minutes
 TST = Total Sleep Time; TIB = Time in Bed; SE = Sleep Efficiency;
 NAASO = Number of Awakenings After Sleep Onset; LPS = Latency to Persistent Sleep;
 WTDS = Wake Time During Sleep; WTAS = Wake Time After Sleep; WASO = Wake After Sleep Onset

Timepoints for the efficacy variables collected during the Phase 3 studies are provided in Table 2.7.3.4 (objective data) and Table 2.7.3.5 (subjective data). Due to the crossover design of the Phase 2 studies SP-0401 and SP-0402, the timepoints (Nights 1 and 2 and Days 2 and 3 of each treatment period) for these studies are not included in the tables. Subjects in these two studies were expected to receive all four treatments (placebo, doxepin 1 mg, 3 mg, and 6 mg).

Table 2.7.3.4 Objective (PSG) Efficacy Analysis Timepoints for Doxepin in the Phase 3 Studies

Study No.	Night 1				Night 15				Night 29				Night 57			Night 85		
	PBO	1 mg	3 mg	6 mg	PBO	1 mg	3 mg	6 mg	PBO	1 mg	3 mg	6 mg	PBO	1 mg	3mg	PBO	1 mg	3 mg
Chronic Insomnia Studies																		
SP-0501	X		X	X	X		X	X	X		X	X						
SP-0503	X	X	X		X	X	X		X	X	X		X	X	X	X	X	X
Transient Insomnia Study																		
SP-0502	X			X														

Notes: X=Study drug evaluated during corresponding clinical study; PBO=placebo.

Shaded boxes indicate not measured/evaluated. SP-0501 and SP-0502 were conducted in adults and SP-0503 was conducted in elderly subjects.

PSG data for SP-0501 also were collected on Nights 2, 16, and 30.

Table 2.7.3.5 Subjective Efficacy Analysis Timepoints for Doxepin in the Phase 3 Studies

Study No.	Day 2				Week 1				Week 2 or Day 16				Week 3		Week 4 or Day 30				Day 58 & Day 86 (Week 12)		
	PBO	1 mg	3 mg	6 mg	PBO	1 mg	3 mg	6 mg	PBO	1 mg	3 mg	6 mg	PBO	6 mg	PBO	1 mg	3 mg	6 mg	PBO	1 mg	3 mg
Chronic Insomnia Studies																					
0501	X		X	X					X		X	X			X		X	X			
0503 ¹	X	X	X		X	X	X		X	X	X				X	X	X		X	X	X
0509 ²					X			X	X			X	X	X	X			X			
Transient Insomnia Study																					
0502	X			X																	

¹ SP-0503 collected subjective efficacy data using the morning questionnaire after each 8-hour PSG recording and the IVRS weekly at home. Data using the IVRS were analyzed by week (Week 1 through Week 12) and by month (Month 1, Month 2, and Month 3). In this SCE, IVRS data for Week 1, Week 4, and Week 12 are presented.

² Outpatient study SP-0509 collected subjective efficacy data using the IVRS daily at home.

Notes: X=Study drug evaluated during corresponding clinical study; PBO=placebo.

Shaded boxes indicate not measured/evaluated. SP-0501 and SP-0502 were conducted in adults and SP-0503 and SP-0509 were conducted in elderly subjects.

Subjective data using the morning questionnaire for SP-0501 also were collected on Days 3, 17, and 31.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

There was no PK assessment conducted in the efficacy studies. In regard to the dose-effectiveness relationship, there seemed to be a trend in both adults and elderly patients that higher doses provided better response. However, this response was not always consistent through out all different variables evaluated, in particularly for sleep onset.

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Table 2.5.4.3 Primary Objective and Subjective Support Variables for Sleep Maintenance – LS Mean Difference from Placebo (Minutes): ITT Analysis Set

Study	Timepoint	Doxepin 1 mg	Doxepin 3 mg	Doxepin 6 mg
Wake After Sleep Onset – Primary Objective Support Variable				
0401	Mean Night 1 & Night 2	-9.6**	-17.2***	-18.2***
0402	Mean Night 1 & Night 2	-18.2***	-27.4***	-33.9***
0501	Night 1 ¹	--	-26.0***	-30.9***
	Night 29	--	-13.8*	-20.7***
0503	Night 1 ¹	-17.8**	-33.8***	--
	Night 85	-13.0*	-26.5***	--
0502	Night 1	--	--	-39.1***
Subjective Total Sleep Time – Primary Subjective Support Variable				
0401	Mean Day 2 & Day 3	-0.7	15.5	16.2*
0402	Mean Day 2 & Day 3	16.3*	23.3***	31.1***
0501	Day 2	--	23.3**	22.0*
	Day 30	--	0.2	9.7
0503	Day 2	-4.0	19.4	--
	Day 86	27.3**	22.5*	--
	Week 1 ²	1.4	34.7**	--
	Week 12 ²	40.7**	53.3***	--
0509	Week 1 ^{2,3}	--	--	28.8***
	Week 4 ²	--	--	24.9***
0502	Day 2	--	--	32.9***

¹ WASO on Night 1 was the primary efficacy analysis for SP-0501 and SP-0503.

² Data collected using an IVRS.

³ sTST at Week 1 was the primary efficacy analysis for SP-0509.

Notes: For WASO, negative values represent improvement relative to placebo. For sTST, positive values represent improvement relative to placebo.

In SP-0401 and SP-0402, WASO measurements taken from Nights 1 and 2 were averaged; if one of the nights had a missing value, the non-missing value was used. For sTST, measurements taken from Days 2 and 3 were averaged; if one of the days had a missing value, the non-missing value was used.

In SP-0501 and SP-0509, missing data were imputed using the LOCF method.

In SP-0503, missing data were imputed using the LOCF method for WASO and for sTST collected using a morning questionnaire; missing baseline values were imputed using the overall population mean for sTST collected using an IVRS.

In SP-0502, the treatment group mean was used to impute missing data for WASO; data presented for sTST were observed.

*p≤0.05; **p≤0.01; ***p≤0.001; all such noted results favor doxepin over placebo.

Source: SP-0401 CSR Post-text Table 8.2 and Post-text Table 25.2; SP-0402 CSR Post-text Table 8.2 and

Post-text Table 25.2; SP-0501 CSR Post-text Table 9.1.3.2 and Post-text Table 34.1.3.2;

SP-0503 CSR Post-text Table 9.1.2, Post-text Table 34.1.2, and Post-text Table 43.2;

SP-0509 CSR Post-text Table 9.1.2; SP-0502 CSR Post-text Table 8.1.2 and Post-text Table 32.1.

Table 2.5.4.4 Results for the Primary Objective and Subjective Support Variables for Sleep Onset: ITT Analysis Set

Study	Timepoint	Placebo	Doxepin 1 mg	Doxepin 3 mg	Doxepin 6 mg
Latency to Persistent Sleep (minutes) – Primary Objective Support Variable					
0401	Mean Night 1 & Night 2	22.0	19.2	19.4	18.7
0402	Mean Night 1 & Night 2	19.0	19.5	15.5	16.4
0501	Night 1	27.0	--	18.1**	16.7***
	Night 29	17.8	--	18.5	16.2
0503	Night 1	27.4	29.1	23.1	--
	Night 85	22.0	20.9	29.5	--
0502	Night 1 ¹	32.9	--	--	19.9***
Latency to Sleep Onset (minutes) – Primary Subjective Support Variable					
0401	Mean Day 2 & Day 3	39.4	35.3	34.3	34.0*
0402	Mean Day 2 & Day 3	31.1	30.9	28.0	25.5*
0501	Day 2	42.7	--	36.1	34.4*
	Day 30	33.0	--	37.9	32.9
0503	Day 2	43.9	49.6	37.1	--
	Day 86	37.6	32.8	38.5	--
	Week 1 ²	48.0	42.6	35.5**	--
	Week 12 ²	43.6	30.1**	34.1*	--
0509	Week 1 ²	60.5	--	--	55.9
	Week 4 ²	52.7	--	--	50.4
0502	Day 2	31.7	--	--	23.4***

¹ LPS on Night 1 was the primary efficacy analysis for SP-0502.

² Data collected using an IVRS.

Notes: Data presented are the geometric LS means, except LPS data for SP-0502, which are the LS means.

In SP-0401 and SP-0402, LPS measurements taken from Nights 1 and 2 were averaged; if one of the nights had a missing value, the non-missing value was used. For LSO, measurements taken from Days 2 and 3 were averaged; if one of the days had a missing value, the non-missing value was used.

In SP-0501 and SP-0509, missing data were imputed using the LOCF method.

In SP-0503, missing data were imputed using the LOCF method for LPS; data presented for LSO collected using a morning questionnaire were observed; missing baseline values were imputed using the overall population mean for LSO collected using an IVRS.

In SP-0502, the treatment group mean was used to impute missing data for LPS; data presented for LSO were observed.

*p≤0.05; **p≤0.01; ***p≤0.001; all such noted results favor doxepin over placebo.

Source: SP-0401 CSR Post-text Table 11.2 and Post-text Table 24.2; SP-0402 CSR Post-text Table 11.2 and

Post-text Table 24.2; SP-0501 CSR Post-text Table 16.1.3.2 and Post-text Table 36.1.3.2;

SP-0503 CSR Post-text Table 17.1.2, Post-text Table 36.1, and Post-text Table 42.2;

SP-0509 CSR Post-text Table 10.1.2; SP-0502 CSR Post-text Table 7.1.2 and Post-text Table 34.1.

Table 2.5.4.5 Primary Objective Support Variable for Prevention of Early Morning Awakenings – LS Mean Difference from Placebo (Percent): ITT Analysis Set

Study	Timepoint	Doxepin 1 mg	Doxepin 3 mg	Doxepin 6 mg
Sleep Efficiency in Hour 8 – Primary Objective Support Variable				
0401	Mean Night 1 & Night 2	9.1**	9.9***	10.7***
0402	Mean Night 1 & Night 2	0.6	9.2**	11.0***
0501	Night 1	--	14.1***	14.3***
	Night 29	--	7.8*	11.1**
0503	Night 1	9.6*	17.4***	--
	Night 85	4.9	7.8	--
0502	Night 1	--	--	10.5***

Notes: For SE in Hour 8, positive values represent improvement relative to placebo.

In SP-0401 and SP-0402, measurements taken from Nights 1 and 2 were averaged. If one of the nights had a missing value, the non-missing value was used.

In SP-0501 and SP-0502, data presented were observed.

In SP-0503, missing data were imputed using the LOCF method.

*p≤0.05; **p≤0.01; ***p≤0.001; all such noted results favor doxepin over placebo.

Source: SP-0401 CSR Post-text Table 9.2.8; SP-0402 CSR Post-text Table 9.2.8; SP-0501 CSR Post-text Table 15.8.3; SP-0503 CSR Post-text Table 15.8.2; SP-0502 CSR Post-text Table 14.8.

2.2.4 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The assay validation and the biosample analysis for doxepin and its metabolite nordoxepin are acceptable. A LC/MS/MS method was developed and validated for measuring the doxepin and nordoxepin concentrations in K2 EDTA human plasma. The LLOQ for both doxepin and nordoxepin were 0.05 ng/mL. The validated concentrations ranged from 0.05- 10.0 ng/mL.

A summary of all methods used is given in the analytical section of this review.

2.2.5 What are the general ADME characteristics of doxepin?

The key ADME characteristics of doxepin are summarized below:

Absorption:

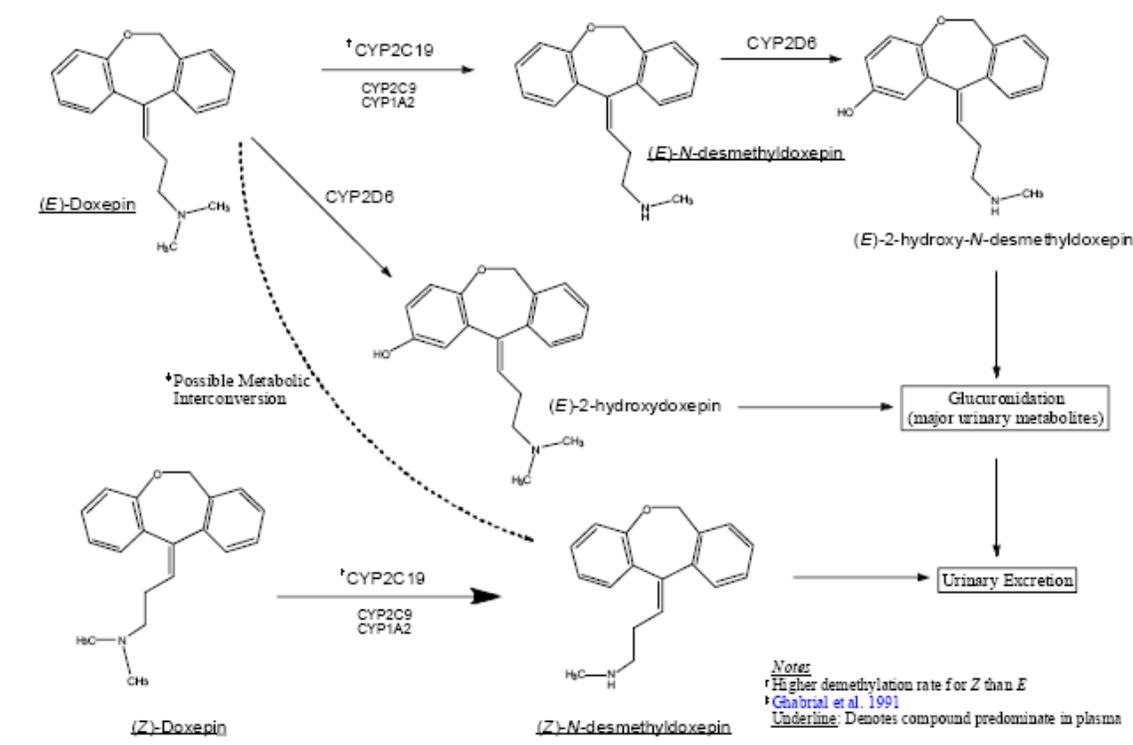
Plasma doxepin concentrations peaked within 3-4 hours postdose whereas the maximum nordoxepin concentrations occur at 6-8 hours and are about 50-75% of doxepin maximum concentrations.

Distribution:

About 80% of doxepin is bound to human plasma proteins. The large Vd/F (over 10,550L) suggests extensive distribution of doxepin into tissues.

Metabolism:

The major metabolic pathways for doxepin are N-demethylation, N-oxidation, hydroxylation and glucuronidation. The major metabolite found in the plasma is nordoxepin, which is an active metabolite for antidepressation shown in the animal studies. The formation of nordoxepin is mainly mediated by CYP 2C19 and to a lesser extent by CYP 1A2 and CYP 2C9. The other important pathway, ring hydroxylation, is extensively mediated by CYP 2D6.



Elimination:

It is predominantly excreted in the urine as the metabolites and/or conjugated metabolites. The elimination t1/2 is approximately 15 hours for doxepin and 31 hours for nordoxepin.

2.2.6 What is the variability in the PK data?

The intersubject variability is very high for doxepin. The high variability in PK parameters is likely due to the high first pass metabolism mediated primarily by CYPs 2D6 and 2C19. This high variability in PK parameters can be influenced by large individual differences in CYP activity. This suggestion is supported by an analysis of inter- and intra-subject variability in Silenor Phase 1 studies, demonstrating substantially smaller variability within subjects compared to that observed between subjects.

Parameter (Unit)	Doxepin	Nordoxepin
AUC _{0-∞} (ng*h/mL)		
Inter-subject CV%	63.0 – 91.7	29.1 – 50.5
Intra-subject CV%	19.4 – 25.5	9.0 – 15.1
C _{max} (ng/mL)		
Inter-subject CV%	43.7 – 79.3	23.0 – 38.6
Intra-subject CV%	18.5 – 30.0	9.0 – 15.6

Data presented are the range of CV% from SP-0405, SP-0504, SP-0505, SP-0506, and SP-0507, obtained from ANOVA models within each study. The source tables provide the terms used in the model for each study. The CV% for nordoxepin AUC_{0-∞} in SP-0405 was not reported due to PK sampling for 48 hours postdose, which was not sufficient to obtain a reliable estimate of λ_z or which resulted in AUC(ext) > 30%.

2.2.7 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The pharmacokinetic parameter, C_{max}, of doxepin appears to be dose proportional within doses of 1 mg, 3 mg and 6 mg. AUC at doses of 3 mg and 6 mg demonstrated the dose proportionality while AUC for 1 mg could not be evaluated due to the limitation of the assay sensitivity. Similar results were seen in nordoxepin. The dose proportionality was not observed in the study comparing 6 mg tablet and 50 mg capsule (Sinequan) utilizing a dose-normalization comparison. Higher C_{max} and AUC were observed in the 50 mg capsule (Sinequan) at a modest extent (~30%).

2.3 INTRINSIC FACTORS

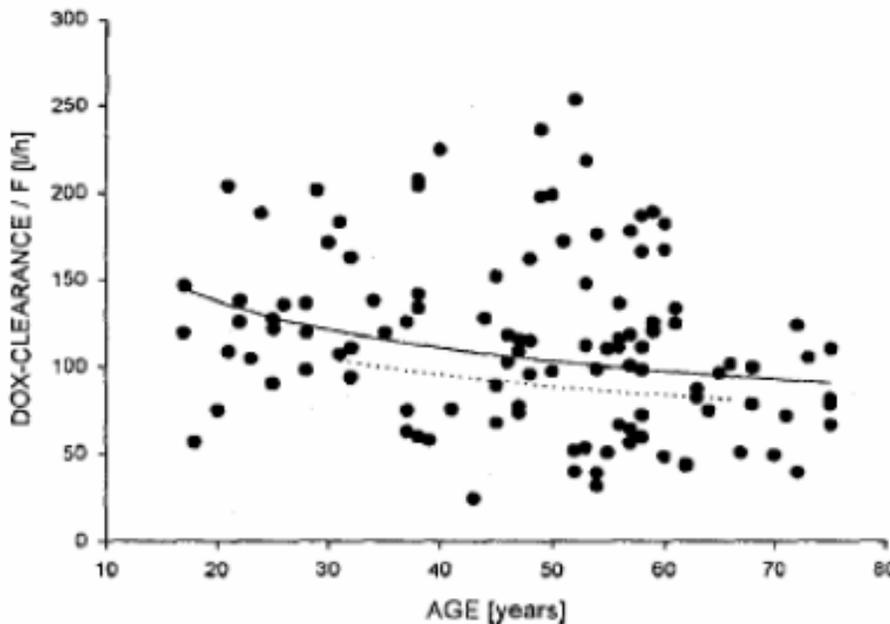
2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.1.1 Effect of age:

Elderly:

No studies were conducted for evaluating the age effect on doxepin PK. Based on a published PPK study, clearance of doxepin was decreased by about one third from age 20 to age 75. In addition, based on the sponsor, elderly patients are more sensitive for sedative drugs; therefore, a lower starting dose was utilized for elderly patients in the Phase III efficacy studies and is also proposed in the sponsor proposed label.



Dosage adjustment:

The initial dose for elderly patients is recommended to be $\frac{(b)}{(4)}$ mg daily while that for adults is $\frac{(b)}{(4)}$ mg daily. Doses for both groups can be increased up to 6 mg daily.

2.3.1.2 Effect of Gender:

Using the pooled data from the five Phase I studies, mean and median C_{max} and AUC were modestly higher in females. However, these differences are not likely to be clinically significant.

Gender	Statistic	AUC _{0-∞} (ng*h/mL)	C _{max} (ng/mL)	T _{max} (h)
Male	n	64	65	65
	Mean (SD)	15.41 (14.906)	0.89 (0.594)	3.41 (1.349)
	Median	9.825	0.646	3
	Min, Max	1.54, 67.5	0.152, 2.54	1, 6
Female	n	36	37	37
	Mean (SD)	16.69 (11.842)	1.04 (0.722)	3.22 (1.289)
	Median	12.2	0.853	3
	Min, Max	4.96, 55.8	0.338, 3.78	1, 6

Data from 6 mg Silenor tablets in the fasted state.

Dosage adjustment:

No dosage adjustment is necessary.

2.3.1.3 Effect of Race:

Using the pooled data from the five Phase I studies, within ethnic groups, there was only enough African-Americans (n=11) to permit an informal comparison to Whites (n=84). Other races were not adequately represented. Higher C_{max} (1.36 vs. 0.90 ng/mL) and AUC (18.5 vs. 15.7 ng*hr/mL) were observed in African-Americans, although the distributions were overlapped. Given the high variability in PK and the wide safety margin of Silenor, the differences observed are not expected to be clinically significant.

Race	Statistic	AUC (0-∞)	AUC (0-24)	C _{max}	T _{max}
White	n	84	85	86	86
	Mean (SD)	15.71 (14.525)	9.98 (7.332)	0.90 (0.642)	3.42 (1.372)
	Median	10.02	7.22	0.6795	3
	Min, Max	1.54, 67.5	1.19, 32.0	0.152, 3.78	1, 6
African American	n	11	11	11	11
	Mean (SD)	18.45 (11.295)	12.92 (6.543)	1.36 (0.677)	3.09 (0.917)
	Median	14.9	11.0	1.14	3
	Min, Max	7.51, 42.7	5.14, 25.6	0.435, 2.25	1.5, 4

Dosage adjustment:

No dosage adjustment is necessary.

2.4 EXTRINSIC FACTORS

2.4.1 Is doxepin a substrate, inhibitor or inducer of CYP enzymes?

Substrate:

Doxepin is a substrate of CYP 2C19 and 2D6 and to a lesser extent for 2C9 and 1A2.

The results of in vitro studies indicate that CYP 2C19 is a key enzyme for N-demethylation of doxepin while 2C9 and 1A2 also play a role in N-demethylation but to a lesser extent. CYP 2D6 is a key enzyme involved in the hydroxylation of doxepin.

Inhibitor:

Based on the in vitro CYP inhibition study (SP-D0118), doxepin is not an inhibitor of human CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2E1) except for weak inhibition of CYP2D6 ($IC_{50}=6.9 \mu\text{M}$ compared with quinidine reference IC_{50} of 86 nM, both using dextromethorphan as the substrate). While clinical study suggested that high dose doxepin (75 to 250 mg/day) might have a mild inhibitory effect on CYP2D6, low doses of doxepin is not expected to have a meaningful inhibitor effect on CYP2D6.

Inducer:

It is not known that whether doxepin is an inducer of any enzymes.

2.4.2 Is doxepin a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

Doxepin is not a substrate of P-gp based on the results of monolayer efflux studies in multidrug resistance transfected MDCK type II cell lines. An efflux ratio of 1.1 for doxepin was determined while the criterion for being a substrate was a ratio of 1.5. Therefore, doxepin would not be considered a P-gp substrate affecting gastrointestinal absorption by this measure.

2.4.3 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.3.1 Influence of doxepin on other drugs:

Effect of doxepin on interacting drug exposure:

Concomitant Medication	Con-med dose	Doxepine dose evaluated	Co-Med Cmax Ratio (90% CI) % change	Co-Med AUC _∞ Ratio (90%CI) % change
Cimetidine	300 mg BID for 2 doses, followed by concomitant doxepin at the 3 rd dose	6 mg SD	NA	NA
Sertraline	50 mg for 7 days	6 mg SD	106 (98-113) ↔	105 (100-110) ↔

- There was no change in steady-state concentrations of sertraline when co-administered with doxepin.

2.4.3.2 Influence of other drugs on doxepin:

Effect of interacting drug on doxepin exposure:

Co-med	Co-med dose	Doxepine dose evaluated	Doxepin Cmax Ratio (90% CI) % change	Doxepin AUC _∞ Ratio (90%CI) % change	Nor-Doxepin Cmax Ratio (90% CI) % change	Nor-Doxepin AUC _∞ Ratio (90%CI) % change	Comment and Dosage Adjustment
Cimetidine	300 mg BID for 2 doses, followed by doxepin at the 3 rd dose	6 mg SD	208 (184-253) 2-fold ↑	198 (174-226) 2-fold ↑	85 (78-92) 15% ↓	101 (93-109) ↔	Exposures of doxepin were doubled Maximum dose of 3 mg in adults and elderly
Sertraline	50 mg for 7 days	6 mg SD	132 (114-152) 32 % ↑	121 (109-133) 21 % ↑	107 (100-114) ↔	122 (115-131) 22 % ↑	PK: No clinically relevant changes in exposure PD: Increased sedation was observed near the Tmax (about 3 hours), but returned to baseline values 6-8 hours post dosing No dose adjustment necessary

- Non-specific CYP 450 inhibitor, cimetidine increases doxepin concentrations in AUC and C_{max} by approximately 2 folds. Dose adjustment: The maximum dose of doxepin in adults and elderly should be 3 mg, when doxepin is co-administered with cimetidine.
- Weak CYP 2D6 inhibitor, sertraline increases doxepin plasma concentrations. AUC_{0-t}, AUC_{0-∞}, and C_{max} of doxepin were approximately 28%, 21%, and 32% higher, respectively, when compared with doxepin alone. Given the variability in doxepin PK, these differences are not likely to be significant. No dose adjustment is necessary.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 **Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

The BCS classification of doxepin has NOT been characterized by the agency although sponsor claimed it to be BCS Class I drug based on its physiochemical properties of high solubility and high intrinsic permeability.

The deficiencies that doxepin could not be classified as BCS class I are summarized below (Please refer to page 89 for details on solubility and permeability information.):

- The (b) (4) titration method was utilized. This is acceptable according to the guidance; however, no justification for the use of this method was provided by the sponsor.
- Complete solubility information at pH 1-7.5 was not provided.
- pK_a information was lacking.
- The sponsor has selected pindolol and atenolol as high and low P markers. However, the suitability of the method was not established based on selected 20 model drugs along with data on their extent of absorption in humans and a plot of the extent of absorption on a function of permeability was not provided.

2.5.2 **Is the proposed to-be-marketed formulation of doxepin bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?**

There are 3 strengths for the to-be-marketed formulations, which are 1, 3 and 6 mg tablets. One bioequivalence study was performed comparing the highest strength, 6 mg to-be-marketed tablet versus 6 mg capsule. The proposed to-be-marketed formulation of 6 mg tablet was shown to be bioequivalent to the 6 mg capsule formulation with the 90% CIs for the ratios of the geometric LS means between two formulations for AUC and C_{max} completely contained in the bioequivalence limits of 80 to 125%.

2.5.3 What is the relative bioavailability of Silenor compared to approved oral doxepin formulations (Sinequan®)?

One relative bioavailability study was performed to compare the to-be-marketed 6 mg tablet to the commercially available 50 mg Sinequin capsule. Due to the difference of the strength and the formulation, a dose-normalization method was utilized for the PK comparison. The proposed to-be-marketed formulation of 6 mg tablet demonstrated approximately 30% lower exposure compared to the approved 50 mg Sinequin based on dose normalization comparison. Mean C_{max} (derived from dose-normalized plasma concentrations) and median T_{max} were approximately 27% lower and 0.5 hour slower, respectively, following administration of doxepin 6 mg when compared with Sinequin 50 mg.

2.5.4 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of doxepin in relation to meals or meal types?

Effect of food on doxepin pharmacokinetics was evaluated by comparing PK of doxepin following a single oral dose of doxepin with or without a high fat meal. The results showed that the high fat food increases doxepin AUC by 41% and C_{max} by 15% and in addition, delayed T_{max} from 3-4 hours to 6-8 hours postdose.

These changes in AUC and T_{max} could affect the onset, maintenance and the next day alertness. In addition, in 5/6 clinical studies, the patients were instructed to take meals at least 1.5 hours before admitting to the clinical sleep laboratory and arrive the site at least 2 hours before bedtime. Based on this, the dose was administered at least 3 hours after their evening meal. However, the instructions for meal time related to the drug administration were not given at the home setting. Therefore it is recommended to not take Silenor within 3 hours of meal intake in stead of sponsor's proposal of not allowing with or immediately after a meal.

Phase II/III	Study number	Patient populations	Duration	Meal time relative to dosing	Place dose administered
II	SP-0401	Adults	2 nights	≥ 3 hours ^a	sleep laboratory ^b
	SP-0402	Elderly	2 nights	≥ 3 hours ^a	sleep laboratory ^b
III	SP-0501	Adults	35 nights	≥ 3 hours ^a	sleep laboratory ^b and self administered at home ^c
	SP-0503	Elderly	85 nights	≥ 3 hours ^a	sleep laboratory ^b and self administered at home ^c
	SP-0502	Healthy adults	1 night	≥ 2.5 hours ^a	sleep laboratory ^b
	SP-0509	Elderly	28 nights	Not indicated	self administered at

					home ^c
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^a: For doses administered at sleep laboratory.

^b: Instructions regarding meal time prior to the admission to the sleep center were provided to the patients.

^c: Guidelines for at home administration relative to meals were not provided.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validation and the biosample analysis for doxepin and its metabolite nordoxepin are acceptable. A LC/MS/MS method was developed and validated for measuring the doxepin and nordoxepin concentrations in K2 EDTA human plasma. The LLOQ for both doxepin and nordoxepin were 0.05 ng/mL. The validated concentrations ranged from 0.05- 10.0 ng/mL. The long-term stability was examined for 19 days for both doxepin and nordoxepin at -70 °C. However, the dates of biosample analysis for each individual studies were not indicated.

A summary of all methods used is presented in the following Table:

Report number	Biological fluid	Analyte	Method	LLOQ	Calibration range	Between-run precision (% CV)	Between-run accuracy (% bias)
YGH00003LX	0.2 mL plasma	Doxepin	LC/MS/MS	0.05 (ng/mL)	0.05; 10 (ng/mL)	< 6.1 %	< 6.6 %
YGH00003LX	0.2 mL plasma	Nordoxepin	LC/MS/MS	0.05 (ng/mL)	0.05; 10 (ng/mL)	< 4.1 %	< 9.3 %
LC 358	0.5 mL plasma	Cimetidine	HPLC-UV	0.01 (µg/mL)	0.01; 10 (µg/mL)	< 10.9 %	< 3.69 %
LCMS 98	0.25 mL plasma	Sertraline	LC/MS/MS	0.1 (ng/mL)	0.1; 50 (ng/mL)	< 6.51 %	< 5.01 %

Adequate concentrations of Quality Controls were used in these assay validations.

3.0 DETAILED LABELING RECOMMENDATION

The reviewer's labeling recommendations are shown by track changes to the sponsor proposed label. These labeling changes should be incorporated in the revised label. The comments for the medical officer in shown in the yellow highlighted text:

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4.0 APPENDIX

4.1 INDIVIDUAL STUDY REVIEW

Study SP-0405: A Pilot Phase 1, Pharmacokinetic Study of Doxepin HCl in Healthy Volunteer

A brief overview of some essential components of the study design is given below:

Study Design	Single-dose, randomized, four-way crossover
Study Population	<p>N=16 <u>Age:</u> 19-34 years (mean 24.1 years) <u>Gender:</u> 16 males <u>Weight:</u> 70.0-110 kg (mean 86.0 kg) <u>Race:</u> White (68.8%), African American (25.0%) and other (6.3%)</p>
Dosage and Administration	<p>Stage I: Subjects were randomized to 6 mg capsule (A) or 6 mg tablet (B) in a treatment sequence (A/B or B/A).</p> <p>Stage II: Subjects were randomized to 3 mg capsule (C) or 1 mg capsule (D) in a treatment sequence (C/D or D/C).</p> <div data-bbox="613 831 1425 999" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <p style="text-align: center;">Stage 1: Periods 1 & 2</p> <p style="text-align: center;">6 mg Tablet → 6 mg Capsule OR 6 mg Capsule → 6 mg Tablet</p> <p style="text-align: center; font-size: 2em;">➔</p> <p style="text-align: center;">Stage 2: Periods 3 & 4</p> <p style="text-align: center;">1 mg Capsule → 3 mg Capsule OR 3 mg Capsule → 1 mg Capsule</p> </div> <p>There was at least 6-day washout period between Treatment period and approximately 2 weeks between Stage I and Stage II.</p> <p>Lot no: 6 mg tablet 3044566 6 mg capsule 3044493 3 mg capsule 3044492 1 mg capsule 3044491</p> <p><u>Diet:</u> Subjects were fasted overnight before dosing and up to 3 hours post-dose.</p> <p>Fluids were restricted from 1 hour predose to 2 hours postdose.</p> <p>Poppy-containing food (e.g., poppy seed bagels, breads, or muffins) was not allowed during the 3 days before any urine drug screen.</p> <p>Alcohol was prohibited for 48 hours before any study visit until 48 hours after dosing.</p> <p>Caffeine-containing products were prohibited for 24 hours before any study visit until 48 hours after dosing.</p>
Sampling: Blood	At predose (0 hour), and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose. The samples were analyzed for plasma concentrations of doxepin and nordoxepin.

Analysis	<p><u>Method</u> LC/MS/MS</p> <p><u>Lower Limits of Quantitation</u></p> <table border="0"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> </tr> <tr> <td>Doxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> <tr> <td>Nordoxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> </table> <p><u>Doxepin:</u> Linear range : 0.05-10.0 ng/mL in plasma Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL) : ≤ 6.1% Inter-day accuracy: -2.7 to -4.7 % Long term Stability: 19 days at -70 °C</p> <p><u>Nordoxepin:</u> Linear range : 0.05-10.0 ng/mL in plasma Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL): ≤ 4.1% Inter-day accuracy: -5.4 to -9.3 % Long term Stability: 19 days at -70 °C</p>		<u>Plasma</u>	Doxepin	0.05 ng/mL	Nordoxepin	0.05 ng/mL
	<u>Plasma</u>						
Doxepin	0.05 ng/mL						
Nordoxepin	0.05 ng/mL						
PK Assessment	AUC _{0-∞} , AUC _{ext} , AUC _{0-t} , AUC ₀₋₂₄ , AUC ₀₋₄₈ , λ _z , C _{max} , T _{max} , t _{1/2} , CL/F, V _d /F						
Safety Assessment	AEs, physical examinations, vital sign measurements (blood pressure, pulse rate, respiratory rate, and temperature), serum chemistry, hematology, urinalysis and 12-lead ECG						

Pharmacokinetic Results:

Doxepin in plasma:

Evaluation of Dose Linearity Within the 1, 3 and 6 mg Capsules:

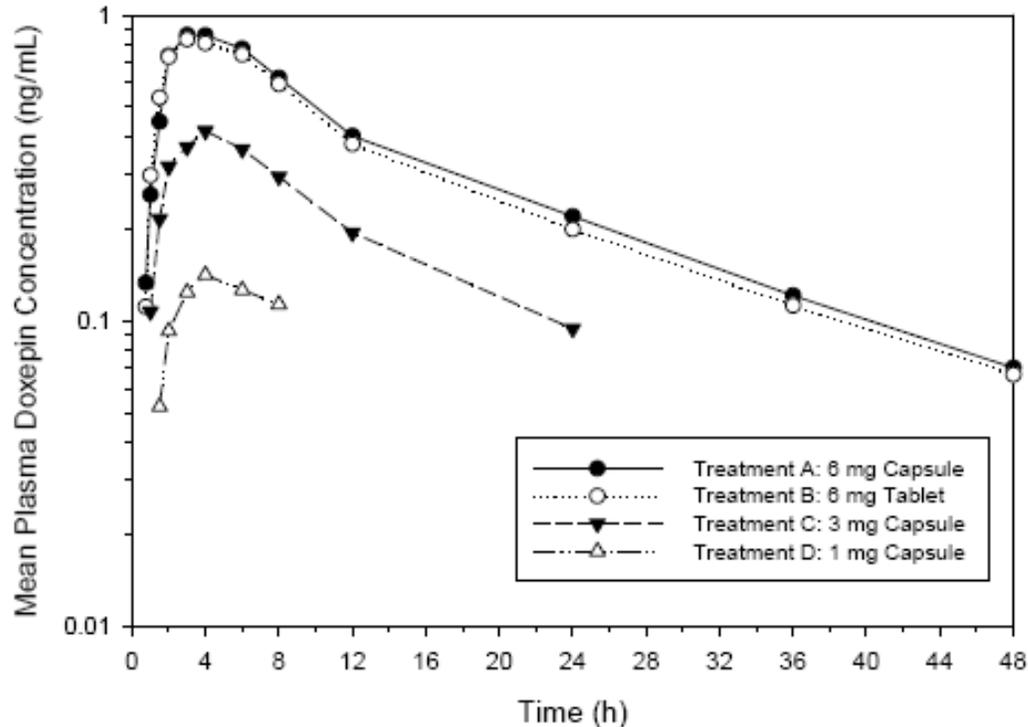
Descriptive Statistics for Doxepin PK Parameters are shown in the following table:

Parameter (Units) [a]	Treatment A 6 mg Capsule	Treatment B 6 mg Tablet	Treatment C 3 mg Capsule	Treatment D 1 mg Capsule
AUC _{0-t} (ng*h/mL)	13.76 (82.9) [n=16]	13.03 (70.8) [n=16]	5.689 (68.9) [n=13]	1.561 (76.7) [n=13]
AUC _{0-∞} (ng*h/mL)	16.26 (81.6) [n=16]	15.19 (69.1) [n=16]	7.518 (64.6) [n=12]	[b] [n=2]
C _{max} (ng/mL)	0.9458 (64.5) [n=16]	0.8864 (59.4) [n=16]	0.4445 (54.0) [n=13]	0.1587 (55.5) [n=15]
T _{max} (h)	4.0 (1.0 – 6.0) [n=16]	3.5 (2.0–6.0) [n=16]	4.0 (1.0–6.0) [n=13]	4.0 (1.5–8.0) [n=14]
λz (1/h)	0.05345 (47.6) [n=16]	0.05534 (76.8) [n=16]	0.05621 (35.5) [n=12]	[b] [n=5]
t _{1/2} (h)	15.13 (41.9) [n=16]	15.32 (31.3) [n=16]	14.28 (46.8) [n=12]	[b] [n=5]
CL/F (L/h)	600.5 (67.5) [n=16]	621.0 (75.1) [n=16]	524.8 (44.4) [n=12]	[b] [n=2]
Vd/F (L)	11040 (45.7) [n=16]	11710 (55.3) [n=16]	9276 (32.2) [n=12]	[b] [n=2]

[a] Estimates presented are the arithmetic means and (CV%) for all of the parameters except T_{max} which is presented using the median and (range).

[b] Parameter could not be accurately calculated.

Mean doxepin concentration-time plot for the 4 different treatments is shown in the following figure:



- The median values of time to maximum plasma doxepin concentration (T_{max}) occurred at 3.5 to 4 hours post dosing across all doses studied.
- C_{max} following administration of 1, 3 and 6 mg capsules showed a dose-proportional increase indicating linear pharmacokinetic within evaluated dose range.
- Several pharmacokinetic parameters for the 1 mg group could not be calculated accurately due to undetectable plasma doxepin concentrations.
- The area under the plasma concentration-time curve (AUC_{0-∞}) showed a 2-fold increase in the 3 mg and 6 mg groups whereas for 1 mg group, the AUC_{0-t} was under estimated and the AUC_{0-∞} was not able to be determined, therefore not accurate to compare with other 2 groups.
- Elimination half-lives (t_{1/2}) range from 14.28 to 15.13 hours for the 3 mg and 6 mg capsules whereas the t_{1/2} could not be calculated in the 1 mg group.
- The CL/F and Vd/F were comparable between the 3 mg and 6 mg doses.

Evaluation of Bioequivalence Between the 6 mg Formulations:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	A	16	11.1	B/A	98.3	(90.7, 107)
	B	16	11.0			
AUC _{0-∞} (ng*h/mL)	A	16	13.6	B/A	97.4	(90.7, 105)
	B	16	13.2			
C _{max} (ng/mL)	A	16	0.827	B/A	93.9	(84.7, 104)
	B	16	0.776			

Treatment A= 6 mg capsule, fasted.

Treatment B= 6 mg tablet, fasted

- T_{max} was slightly delayed following administration of Treatment A (4.0 hours) compared to Treatment B (3.5 hours).
- The mean t_{1/2} of Treatment A (15.13 hours) was nearly identical to Treatment B (15.32 hours).
- The 90% CIs for the ratios of the geometric LS means were completely contained within the equivalent range of 80% to 125 % for AUC_{0-t} (90.7, 107), AUC_{0-∞} (90.7, 105), and C_{max} (84.7, 104). The 6 mg tablet and 6 mg capsule are bioequivalent.

Metabolite in plasma (Nordoxepin):

Evaluation of Dose Linearity Between the 1, 3 and 6 mg Capsules:

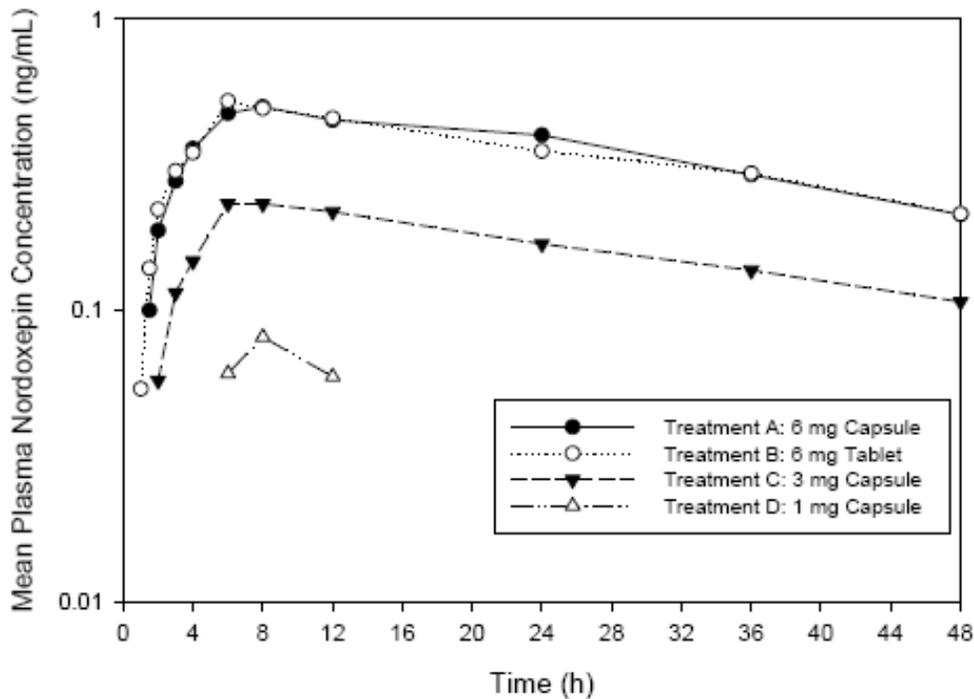
Descriptive Statistics for Nordoxepin PK Parameters are shown in the following table:

Parameter (Units) [a]	Treatment A 6 mg Capsule	Treatment B 6 mg Tablet	Treatment C 3 mg Capsule	Treatment D 1 mg Capsule
AUC _{0-t} (ng*h/mL)	16.34 (46.1) [n=16]	16.23 (40.0) [n=16]	7.573 (47.8) [n=15]	2.271 (57.5) [n=8]
AUC _{0-∞} (ng*h/mL)	[b] [n=2]	17.57 (27.5) [n=3]	13.0 (69.4) [n=5]	[b] [n=0]
C _{max} (ng/mL)	0.4945 (30.9) [n=13]	0.5586 (34.0) [n=16]	0.2539 (38.7) [n=15]	0.08731 (32.9) [n=15]
T _{max} (h)	6.0 (4.0–24.0) [n=13]	8.0 (6.0–12.0) [n=16]	6.0 (4.0–12.0) [n=15]	8.0 (4.0–12.0) [n=14]
λ _z (1/h)	0.02399 (26.5) [n=15]	0.02288 (21.1) [n=13]	0.02433 (27.0) [n=12]	0.01870 (44.1) [n=3]
t _{1/2} (h)	30.64 (24.6) [n=15]	31.68 (22.5) [n=13]	30.70 (30.4) [n=12]	[b] [n=3]

[a] Estimates presented are the arithmetic means and (CV%) for all parameters except T_{max} which is presented using the median and (range).

[b] Parameter could not be calculated accurately.

Mean nordoxepin concentration-time plot for the 4 different treatments is shown in the following figure:



- The median values of time to maximum plasma nordoxepin concentration (T_{max}) occurred at 6 to 8 hours post dosing across all doses studied.
- C_{max} following administration of 1, 3 and 6 mg capsules increased proportionally with dose.

- Several pharmacokinetic parameters could not be estimated due to insufficient number of samples with detectable plasma nordoxepin concentrations.
- Similar to doxepin, AUC_{0-t} for nordoxepin increased proportionally between 3 and 6 mg. However, due to the under estimation of AUC_{0-t} for administration of 1 mg, dose proportionality could not be established from 1 to 6 mg.
- t_{1/2} of nordoxepin is approximately 31 hours for the 3 mg and 6 mg capsules whereas the t_{1/2} could not be calculated in the 1 mg group.

Evaluation of Bioequivalence Between the 6 mg Formulations:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	A	16	15.6	B/A	101	(96.0, 106)
	B	16	15.7			
C _{max} (ng/mL)	A	13	0.531	B/A	104	(93.6, 116)
	B	16	0.554			

Treatment A= 6 mg capsule, fasted.

Treatment B= 6 mg tablet, fasted

- T_{max} of nordoxepin occurred 2 hours earlier following administration of Treatment A (6.0 hours) compared to Treatment B (8.0 hours).
- The mean t_{1/2} of Treatment A (30.64 hours) was similar to Treatment B (31.68 hours).
- The 90% CIs for the ratios of the geometric LS means were completely contained within the equivalent range of 80% to 125 % for AUC_{0-t} (96.0, 106) and C_{max} (93.6, 116).

Conclusions:

- For both doxepin and its metabolite, nordoxepin, the C_{max} were found to be dose proportional across the studied dose range of 1, 3 and 6 mg. There was 6-fold increase between doses of 1 to 6 mg.
- The exposure (AUC) was proportional between doses of 3 and 6 mg for both doxepin and nordoxepin whereas the proportionality could not be assessed across all 3 dose levels down to 1 mg due to under estimation of the AUC_{0-t} for 1 mg group.
- The C_{max} and AUC for 6 mg tablet and 6 mg capsule were comparable. The 90% CIs for the ratios of the geometric LS means between these two formulations were completely contained within the equivalence limits of 80% to 125% for both doxepin and nordoxepin suggesting bioequivalence between 6 mg tablet and 6 mg capsule.
- T_{max} were 3.5- 4 hours for doxepin and 6-8 hours for nordoxepin.
- t_{1/2} were approximately 15 hours for doxepin and 31 hours for nordoxepin.
- CL/F and Vd/F were comparable between the 3 mg and 6 mg doses for doxepin.

Reviewer's Comment:

- *While $AUC_{0-t}/AUC_{0-\infty}$ for both 6 mg formulations were sufficient, the percentages for 3 mg and 1 mg capsule were just over 75% and 58%, respectively, which is generally considered too low for an adequate PK profile. However, since AUC data from the 1 mg capsule was not used for evaluation and in light of the limitation of the assay sensitivity with LLOQ of 0.05ng/mL, using C_{max} for the dose linearity evaluation is considered acceptable.*

Study SP-0504: A Randomized, Open-Label Study to Assess the Effect of Food on the Pharmacokinetics of Doxepin HCl

A brief overview of some essential components of the study design is given below:

Study Design	Randomized, open-label, single dose, two-way cross over				
Study Population	N=16 <u>Age:</u> 20-32 years (mean 24.4 years) <u>Gender:</u> 16 males and females (10M/6F) <u>Weight:</u> 50.2-109.5 kg (mean 70.94 kg) <u>Race:</u> White (87.5%), African-American (6.3%) and Hispanic (6.3%)				
Dosage and Administration	Subjects were randomized into one of two treatment sequences (fed/fasted or fasted/fed). 6 mg tablet was administered with the fed or fasted condition assigned. There was a 7-day washout period between Treatment periods. Lot no: 6 mg tablet 3044566 <u>Diet:</u> Subjects dosed under fasting conditions were required to fast overnight for at least 10 hours prior to study drug administration and for 4 hours postdose. Subjects dosed under fed conditions were dosed 5 minutes after a standardized high-fat, high-calorie breakfast. Fluids were restricted from 1 hour predose to 1 hour postdose. Poppy-containing food (e.g., poppy seed bagels, breads, or muffins) was not allowed during the 3 days before any urine drug screen. Alcohol was prohibited for 48 hours before any study visit until 48 hours after dosing. Caffeine-containing products were prohibited for 24 hours before any study visit until 48 hours after dosing.				
Sampling: Blood	At predose (0 hour), and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours postdose. The samples were analyzed for plasma concentrations of doxepin and nordoxepin.				
Analysis	<u>Method</u> LC/MS/MS <u>Lower Limits of Quantitation</u> <table style="margin-left: 40px;"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> </tr> <tr> <td>Doxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> </table> Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL) : ≤ 6.1% Inter-day accuracy: -2.7 to -4.7 % Long term Stability: 19 days at -70 °C		<u>Plasma</u>	Doxepin	0.05 ng/mL
	<u>Plasma</u>				
Doxepin	0.05 ng/mL				

	Nordoxepin 0.05 ng/mL Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL): ≤ 4.1% Inter-day accuracy: -5.4 to -9.3 % Long term Stability: 19 days at -70 °C
PK Assessment	AUC _{0-t} , AUC ₀₋₂₄ , AUC ₀₋₄₈ , AUC ₀₋₇₂ , AUC ₀₋₉₆ , AUC _{0-∞} , C _{max} , T _{max} , λ _z and t _{1/2} for both doxepin and nordoxepin The following PK parameters were assessed for doxepin only: CL/F and Vd/F
Safety Assessment	AEs, physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (serum chemistry, hematology, and urinalysis etc

Pharmacokinetic Results:

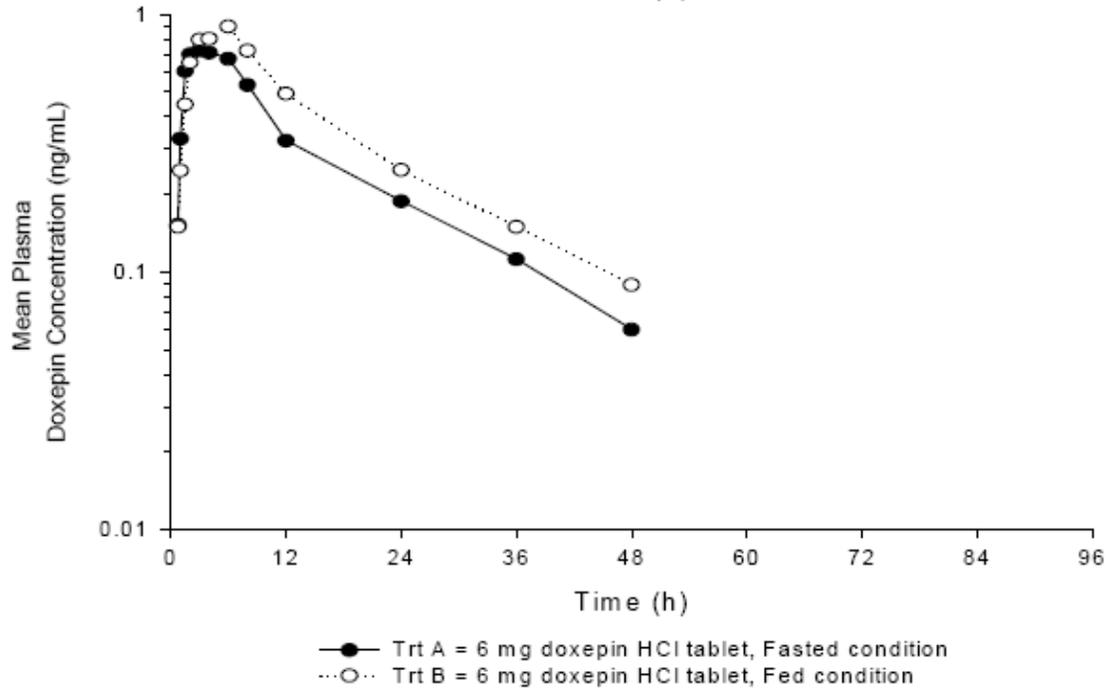
Doxepin in plasma:

Descriptive Statistics for Doxepin PK Parameters are shown in the following table:

Parameter (unit)	Treatment A Doxepin 6 mg, Fasted (N=15)	Treatment B Doxepin 6 mg, Fed (N=16)
AUC _{0-t} (ng*h/mL)	12.57 (85.7)	16.81 (74.0)
AUC _{0-∞} (ng*h/mL)	14.12 (80.6)	18.55 (70.2)
C _{max} (ng/mL)	0.8544 (63.2)	0.9514 (58.8)
T _{max} (h)	3.0 (1.5-6.0)	6.0 (2.0-6.0)
λ _z (1/h)	0.0623 (65.9)	0.0444 (26.6)
t _{1/2} (h)	14.37 (42.2)	16.53 (23.8)
CL/F (L/h)	837.1 (114.3)	477.4 (63.4)
Vd/F (L)	11930 (46.9)	10280 (43.3)

The data presented are the arithmetic mean and (CV%) for all parameters except T_{max} which is presented by median (range).

Mean doxepin concentration-time plot for each of the treatments is shown in the following figure:



Statistical Comparison of Doxepin PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	A	15	9.194	B/A	145.6	(127.0, 166.9)
	B	16	13.39			
AUC _{0-∞} (ng*h/mL)	A	15	10.72	B/A	141.3	(124.7, 160.1)
	B	16	15.14			
C _{max} (ng/mL)	A	15	0.7170	B/A	114.6	(101.8, 129.1)
	B	16	0.8220			

Treatment A= doxepin 6 mg tablet, fasted.

Treatment B= doxepin 6 mg tablet, fed

- AUC_{0-t}, AUC_{0-∞}, and C_{max} of doxepin increased by 34%, 32%, and 11%, respectively, under fed conditions compared to the fasted condition.
- The median T_{max} was delayed by 3.0 hours in the fed condition although the range was similar for both treatment conditions.
- The mean t_{1/2} was delayed approximately 2 hours in the fed condition.
- Mean CL/F and Vd/F were 43% and 14% lower in the fed condition compared to the fasted condition, respectively.
- The 90% CIs for the ratios of the geometric LS means between the treatments were not completely contained within the equivalence limits of 80% to 125% for C_{max} (101.8, 129.1). The 90% CIs were above the equivalence limits for AUC_{0-t} (127.0, 166.9) and AUC_{0-∞} (124.7, 160.1) indicating that high-fat meal significantly affected the PK profile of doxepin.

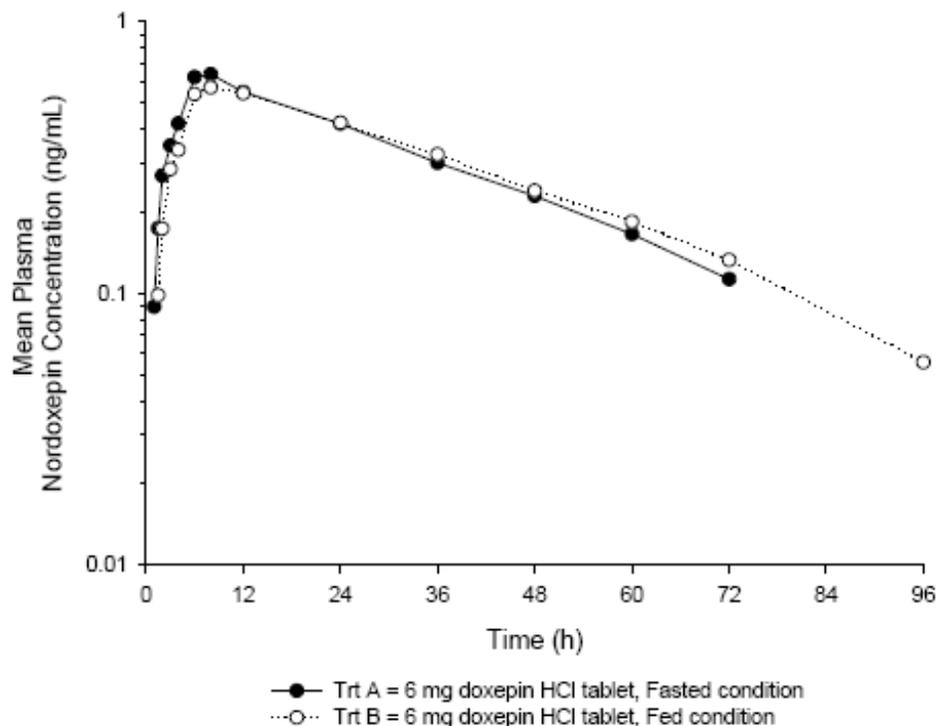
Nordoxepin in plasma:

Descriptive Statistics for nordoxepin PK Parameters are shown in the following table:

Parameter (unit)	Treatment A Doxepin 6 mg, Fasted (N=15)	Treatment B Doxepin 6 mg, Fed (N=16)
AUC _{0-t} (ng*h/mL)	24.19 (54.0)	24.56 (46.2)
AUC _{0-∞} (ng*h/mL)	27.45 (53.0)	28.39 (43.9)
C _{max} (ng/mL)	0.6530 (34.0)	0.5981 (32.4)
T _{max} (h)	8.0 (6.0-12.0)	8.0 (6.0-12.0)
t _{1/2} (h)	25.06 (19.5)	27.82 (20.9)
λ _z (1/h)	0.02870 (21.1)	0.02587 (19.3)

The data presented are the arithmetic mean and (CV%) for all parameters except T_{max} which is presented by median (range).

Mean nordoxepin concentration-time plot for each of the treatments is shown in the following figure:



Statistical Comparison of Nordoxepin PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	A	15	21.76	B/A	102.1	(94.8, 110.0)
	B	16	22.23			
AUC _{0-∞} (ng*h/mL)	A	15	25.02	B/A	104.0	(97.1, 111.4)
	B	16	26.02			
C _{max} (ng/mL)	A	15	0.6195	B/A	91.6	(86.4, 97.1)
	B	16	0.5675			

Treatment A= doxepin 6 mg tablet, fasted.

Treatment B= doxepin 6 mg tablet, fed

- Pharmacokinetic parameters of nordoxepin, AUC_{0-t}, AUC_{0-∞}, C_{max}, T_{max}, λ_z and t_{1/2} were similar in fed and fasted condition.
- The 90% CIs for the ratios of the geometric LS means between the fed and fasted treatments were completely contained within the equivalence limits of 80% to 125% for AUC_{0-t}, AUC_{0-∞}, and C_{max} indicating that high-fat meal did not significantly alter the nordoxepin PK profile.

Dose administration in relation to the meal time in clinical trials:

Phase II/III	Study number	Patient populations	Duration	Meal time relative to dosing	Place dose administered
II	SP-0401	Adults	2 nights	≥ 3 hours ^a	sleep laboratory ^b
	SP-0402	Elderly	2 nights	≥ 3 hours ^a	sleep laboratory ^b
III	SP-0501	Adults	35 nights	≥ 3 hours ^a	sleep laboratory ^b and self administered at home ^c
	SP-0503	Elderly	85 nights	≥ 3 hours ^a	sleep laboratory ^b and self administered at home ^c
	SP-0502	Healthy adults	1 night	≥ 2.5 hours ^a	sleep laboratory ^b
	SP-0509	Elderly	28 nights	Not indicated	self administered at home ^c

^a: For doses administered at sleep laboratory.

^b: Instructions regarding meal time prior to the admission to the sleep center were provided to the patients.

^c: Guidelines for at home administration relative to meals were not provided.

- In 5/6 clinical studies, the patients were instructed to take meals at least 1.5 hours before admitting to the clinical sleep laboratory and arrive the site at least 2 hours before bedtime. Based on this, the dose was administered at least 3 hours after their evening meal.
- The instructions for meal time in relation to the drug were not given at the home setting.

Conclusions:

- A significant food effect for doxepin was evident when doxepin was administered with high-fat meal. C_{max} and AUC_{0-∞} were significantly increased by about 15% and 41 %, respectively, under the fed condition.
- T_{max} was delayed for 3 hours and the t_{1/2} was prolonged for 2 hours under the fed conditions.
- No food effect was observed for the metabolite of doxepin, nordoxepin, when doxepin was administered with food.
- Doses were given at least 3 hours after the evening meal in clinical trials.
- For the indication of insomnia, doxepin is recommended to not be taken within 3 hours of meal intake.

Reviewer's comment:

- *The sponsor proposed that doxepin [REDACTED] (b) (4) [REDACTED]. However, this doesn't reflect the conditions in the clinical studies for drug administration and doesn't rule out the possibility of food effect since this could mislead the patients to take the drug like 30 minutes after their meal which would introduce the food effect. Therefore doxepin is recommended to not be taken within 3 hours of meal intake.*
- *In the clinical trials at the home settings, since the dosing instructions were not given to the patients, the dosing in relation to the meal time is not certain. Based on this, the possibility of the adverse events or the second day effect for the self-dosing portion could be different from the portion conducted at the sleep laboratory.*

Study SP-0505: A Fixed Sequence, Open-Label Study to Assess the Pharmacokinetic Interaction of Cimetidine with Doxepin HCl in Healthy Adult Subjects

This study was conducted in order to assess the effect of cimetidine on the PK profile of doxepin 6 mg. Doxepin is metabolized, in part, by CYP2D6. Cimetidine is known to inhibit CYP2D6 and interact with doxepin as shown in the existing product information (Sinequan®). However, clinical trials demonstrating this interaction studied doxepin doses from 50 mg to 100 mg. No study data exist currently assessing a cimetidine drug interaction with low doses of doxepin.

A brief overview of some essential components of the study design is given below:

Study Design	Fixed sequence, open-label, drug interaction study												
Study Population	<p>N=24 <u>Age:</u> 18-42 years (mean 24 years) <u>Gender:</u> 24 males and females (9M/15F) <u>Weight:</u> 50-93 kg (mean 71.04 kg) <u>Race:</u> White (87.5%), African-American (8.3%) and other (Multiracial) (4.2%)</p>												
Dosage and Administration	<p>Subjects received 2 Treatments with a fixed sequence. Period 1(Treatment A): single oral dose of 6 mg tablet under fasted condition Period 2 (Treatment B): One day prior to the 6 mg doxepin administration, one 300 mg cimetidine tablet was dosed in the morning and one in the evening. On the treatment day, 6 mg doxepine tablet was co-administered with one 300 mg cimetidine in the morning under fasted condition. Additional 300 mg cimetidine tablets were dosed in the evening on the same day and in the morning on the following day. There was a 7-day washout period between Treatment periods.</p> <table border="1" data-bbox="602 1304 1430 1436"> <thead> <tr> <th data-bbox="607 1310 797 1331">Treatment Period 1</th> <th colspan="3" data-bbox="1034 1310 1425 1331">Treatment Period 2</th> </tr> <tr> <th data-bbox="607 1337 797 1358">Day 1</th> <th data-bbox="802 1337 1040 1358">Day 8</th> <th data-bbox="1045 1337 1321 1358">Day 9</th> <th data-bbox="1326 1337 1425 1358">Day 10</th> </tr> </thead> <tbody> <tr> <td data-bbox="607 1362 797 1383">Doxepin 6 mg (a.m.)</td> <td data-bbox="802 1362 1040 1411">Cimetidine 300 mg (a.m.) Cimetidine 300 mg (p.m.)</td> <td data-bbox="1045 1362 1321 1436">Doxepin 6 mg + Cimetidine 300 mg (a.m.) Cimetidine 300 mg (p.m.)</td> <td data-bbox="1326 1362 1425 1436">Cimetidine 300 mg (a.m.)</td> </tr> </tbody> </table> <p>Doxepin lot no: 6 mg tablet 3044566 Tagamet® (cimetidine) lot no: 300 mg tablets Y25T13</p> <p><u>Diet:</u> Subjects were required to fast overnight for at least 10 hours prior to study drug administration for Treatment A and Treatment B and for 4 hours postdose. Fluids were restricted from 1 hour predose to 1 hour postdose.</p> <p>Poppy-containing food (e.g., poppy seed bagels, breads, or muffins) was not allowed during the 3 days before any urine drug screen.</p>	Treatment Period 1	Treatment Period 2			Day 1	Day 8	Day 9	Day 10	Doxepin 6 mg (a.m.)	Cimetidine 300 mg (a.m.) Cimetidine 300 mg (p.m.)	Doxepin 6 mg + Cimetidine 300 mg (a.m.) Cimetidine 300 mg (p.m.)	Cimetidine 300 mg (a.m.)
Treatment Period 1	Treatment Period 2												
Day 1	Day 8	Day 9	Day 10										
Doxepin 6 mg (a.m.)	Cimetidine 300 mg (a.m.) Cimetidine 300 mg (p.m.)	Doxepin 6 mg + Cimetidine 300 mg (a.m.) Cimetidine 300 mg (p.m.)	Cimetidine 300 mg (a.m.)										

	<p>Alcohol was prohibited for 48 hours before any study visit until 48 hours after dosing.</p> <p>Caffeine-containing products were prohibited for 24 hours before any study visit until 48 hours after dosing.</p>										
Sampling: Blood	<p>Plasma samples were collected at predose (0 hour), and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours postdose. All timepoints were used for analysis of doxepin and nordoxepin plasma concentrations while timepoints at 0 through 24 hours postdose of Treatment B during Treatment Period 2 were used for analysis of cimetidine concentrations in plasma.</p>										
Analysis	<p><u>Method</u> Doxepin and nordoxepin: LC/MS/MS <u>Lower Limits of Quantitation</u></p> <table border="0"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> </tr> <tr> <td>Doxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> </table> <p>Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL) : ≤ 6.1% Inter-day accuracy: -2.7 to -4.7 % Long term Stability: 19 days at -70 °C</p> <table border="0"> <tr> <td>Nordoxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> </table> <p>Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL): ≤ 4.1% Inter-day accuracy: -5.4 to -9.3 % Long term Stability: 19 days at -70 °C</p> <p>Cimetidine: HPLC-UV <u>Lower Limits of Quantitation</u></p> <table border="0"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> </tr> <tr> <td>Cimetidine</td> <td style="text-align: center;">0.01 µg/mL</td> </tr> </table> <p>Inter-day Precision (%CV for Quality Controls) : ≤ 6.66% Inter-day accuracy: -3.69 to +2.59 % Short term Stability: 7 days at -20 °C</p>		<u>Plasma</u>	Doxepin	0.05 ng/mL	Nordoxepin	0.05 ng/mL		<u>Plasma</u>	Cimetidine	0.01 µg/mL
	<u>Plasma</u>										
Doxepin	0.05 ng/mL										
Nordoxepin	0.05 ng/mL										
	<u>Plasma</u>										
Cimetidine	0.01 µg/mL										
PK Assessment	<p>AUC_{0-t}, AUC₀₋₂₄, AUC₀₋₄₈, AUC₀₋₇₂, AUC₀₋₉₆, AUC_{0-∞}, C_{max}, T_{max}, λ_z and t_{1/2} for doxepin and nordoxepin The following PK parameters were assessed for doxepin only: CL/F and V_d/F No PK parameters were derived for cimetidine.</p>										
Safety Assessment	<p>AEs, physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (serum chemistry, hematology, and urinalysis etc</p>										

Pharmacokinetic Results:

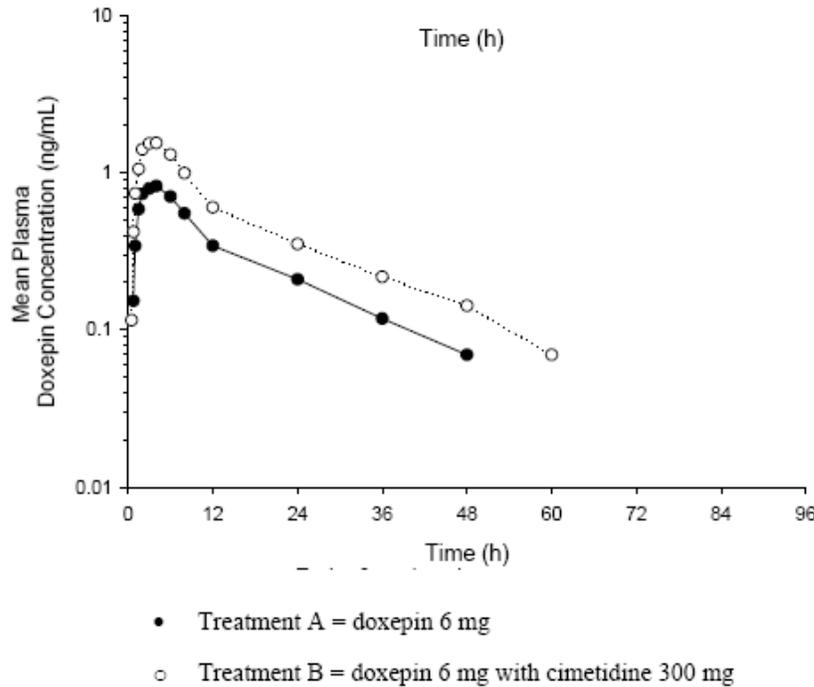
Doxepin in plasma:

Descriptive Statistics for Doxepin PK Parameters are shown in the following table:

Parameter (Unit)	Treatment A (Doxepin 6 mg) N=24	Treatment B (Doxepin 6 mg + Cimetidine 300 mg) N=22
AUC _{0-t} (ng*h/mL)	14.28 (93.4) n=23	25.77 (68.0) n=22
AUC _{0-∞} (ng*h/mL)	15.99 (90.6) n=23	27.67 (67.2) n=22
C _{max} (ng/mL)	0.8645 (57.1) n=24	1.701 (42.6) n=22
T _{max} (h)	4.0 (1.5–6.0) n=24	3.0 (2.0–6.0) n=22
t _{1/2} (h)	15.93 (43.6) n=23	16.79 (26.6) n=22
λ _z (1/h)	0.05031 (36.2) n=23	0.04391 (24.6) n=22
CL/F (L/h)	607.5 (59.2) n=23	286.6 (48.0) n=22
Vd/F (L)	11690 (46.2) n=23	6356 (35.1) n=22

The data presented are the arithmetic mean (CV%) for all parameters except T_{max} which is presented by median (range).

Mean doxepin concentration-time plot for each of the treatments is shown in the following figure:



Statistical Comparison of Doxepin PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-∞} (ng*h/mL)	A	23	12.11	B/A	198.0	(173.9, 225.5)
	B	22	23.98			
C _{max} (ng/mL)	A	24	0.7482	B/A	208.1	(184.0, 235.3)
	B	22	1.557			

Treatment A= doxepin 6 mg, fasted; Treatment B= doxepin 6 mg + cimetidine 300 mg, fasted.

- 2 fold increases in doxepin AUC_{0-∞} and C_{max} was observed when doxepin was coadministered with cimetidine.
- The median T_{max} was 1 hour earlier when coadministered with cimetidine.
- The mean t_{1/2} was similar between two treatments with or without co-administration of cimetidine.
- The 90% CIs for the ratios of the geometric LS means between Treatment A (doxepin 6 mg) and Treatment B (doxepin 6 mg with cimetidine 300 mg) were above the equivalence limits of 80% to 125% for AUC_{0-∞} (173.9, 225.5) or C_{max} (184.0, 235.3).

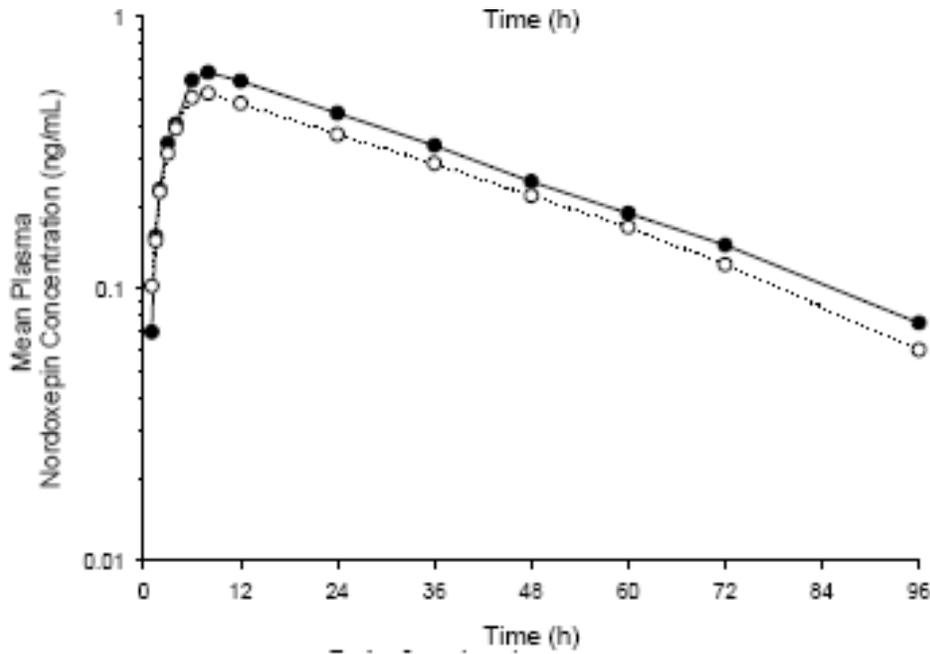
Nordoxepin in plasma:

Descriptive Statistics for Nordoxepin PK Parameters are shown in the following table:

Parameter (Unit)	Treatment A (Doxepin 6 mg) N=24	Treatment B (Doxepin 6 mg + Cimetidine 300 mg) N=22
AUC ₀₋₄ (ng*h/mL)	26.66 (54.0) n=23	22.83 (30.9) n=20
AUC _{0-∞} (ng*h/mL)	26.03 (31.8) n=21	26.15 (30.2) n=20
C _{max} (ng/mL)	0.6523 (33.2) n=24	0.5355 (27.2) n=20
T _{max} (h)	8.0 (6.0–12.0) n=24	8.0 (4.0–12.0) n=20
t _{1/2} (h)	28.64 (39.9) n=23	28.54 (17.7) n=20
λ _z (1/h)	0.02671 (26.8) n=23	0.02501 (18.1) n=20

The data presented are the arithmetic mean (CV%) for all parameters except T_{max} which is presented by median (range).

Mean nordoxepin concentration-time plot for each of the treatments is shown in the following figure:



- Treatment A = doxepin 6 mg
- Treatment B = doxepin 6 mg with cimetidine 300 mg

Statistical Comparison of Nordoxepin PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-∞} (ng·h/mL)	A	21	24.80	B/A	100.8	(92.9, 109.4)
	B	20	25.00			
C _{max} (ng/mL)	A	24	0.6211	B/A	84.8	(78.0, 92.3)
	B	20	0.5269			

Treatment A= doxepin 6 mg, fasted; Treatment B= doxepin 6 mg + cimetidine 300 mg, fasted.

- AUC_{0-∞} were similar in the treatments with or without cimetidine coadministration.
- C_{max} was 18% lower when coadministered with cimetidine.
- T_{max} were 8 hours post dosing and t_{1/2} were almost identical in both treatments.
- The 90% CIs for the ratios of the geometric LS means between Treatment A (doxepin 6 mg) and Treatment B (doxepin 6 mg with cimetidine 300 mg) were contained completely within the equivalence limits of 80% to 125% for AUC_{0-∞} (92.9, 109.4) but outside the lower equivalence limits for C_{max} (78.0, 92.3).

Conclusions:

- A significant drug interaction was observed when doxepin was coadministered with cimetidine. C_{max} and AUC of doxepin were increased by 2 folds in the cimetidine coadministration treatment group.
- Coadministration with cimetidine did not markedly alter the nordoxepin PK profile. AUC were contained in the equivalence limit while C_{max} following the coadministration was slightly outside the lower equivalence limit.

Reviewer's Comment:

- *PK parameters of cimetidine were not derived. By looking at the plasma concentration-time profile, most subjects have similar or slightly higher cimetidine concentrations at 24 h than at 12h. This is reasonable according to the BID dosing regimen where 0 to 12 hours represent one dosing interval while the data at 24 hours represent a trough level and no samples were collected between 12 to 24 hours. Since only the PK profile following coadministration was collected and the effect of doxepin on cimetidine was not evaluated, no further comparison and conclusion could be made at this time.*
- *Although the highest dose of doxepin for insomnia is much lower than depression (6 mg vs. 150 mg), concomitant administration of cimetidine shows a 2-fold increase in doxepin exposure. These exposures are greater at all time points. The increased exposure of doxepin following cimetidine co-administration, specifically at 6 and 8 hours are of concern for the next day residual effects of doxepin. The mean doxepin plasma concentrations were 0.70 vs 1.30 ng/mL (doxepin alone vs doxepin+cimetidine) and 0.55 vs 0.99 ng/mL (doxepin alone vs doxepin+cimetidine), respectively, at 6 and 8 hours post dosing. These increased concentrations following co-administration were even higher than the C_{max} (0.86 ng/mL) after doxepin alone. Therefore there is a concern of second day residual effect which might be caused by the high plasma levels at 6-8 hours post dosing when co-administered with cimetidine. A dose adjustment should be considered when cimetidine is concomitantly used.*

Dose adjustment:

The maximum dose of doxepin in adults and elderly should be 3 mg, when doxepin is co-administered with cimetidine.

Study SP-0506: A Single-Blind Study to Assess the Pharmacodynamic and Pharmacokinetic Interaction of Sertraline HCl with Doxepin HCl in Healthy Adult Subjects

Depression is a common comorbidity in insomnia patients. Therefore, coadministration of an antidepressant, such as a selective serotonin reuptake inhibitor (SSRI), with doxepin for the treatment of insomnia might be anticipated. Of concern would be a PK/PD interaction whereby additive or synergistic cognitive and/or sedative impairments might result from such combination treatment. This study was conducted primarily in order to assess the effect of sertraline, an SSRI, on the PK, PD, and PK/PD profiles of doxepin.

A brief overview of some essential components of the study design is given below:

Study Design	single-blind, double-dummy, fixed sequence, drug interaction study																			
Study Population	<p>N=24 <u>Age:</u> 19-44 years (mean 26 years) <u>Gender:</u> 24 males and females (16M/8F) <u>Weight:</u> 58-104.5 kg (mean 78.06 kg) <u>Race:</u> White (83.3%), African-American (8.3%) and Asian (8.3%)</p>																			
Dosage and Administration	<p>Subjects received 3 Treatments (A, B and C) in 2 Periods with a fixed sequence.</p> <p>Period 1(Treatment A): single oral dose of 6 mg doxepin tablet and sertraline placebo under fasted condition on Day 1. Then 50 mg sertraline and doxepin placebo once daily in the morning under fasted condition on Day 8 through Day 13.</p> <p>Period 2 (Treatment B): 50 mg sertraline and doxepin placebo on Day 14 under fasted condition.</p> <p>Period 2 (Treatment C): 50 mg sertraline and 6 mg doxepin tablet on Day 15 under fasted condition.</p> <table border="1" data-bbox="602 1213 1437 1480"> <thead> <tr> <th colspan="2" data-bbox="602 1213 1015 1255">Treatment Period 1</th> <th colspan="2" data-bbox="1015 1213 1437 1255">Treatment Period 2</th> </tr> <tr> <th data-bbox="602 1255 808 1283">Day 1</th> <th data-bbox="808 1255 1015 1283">Days 8-13</th> <th data-bbox="1015 1255 1230 1283">Day 14</th> <th data-bbox="1230 1255 1437 1283">Day 15</th> </tr> </thead> <tbody> <tr> <td data-bbox="602 1283 808 1339">Sertraline Placebo + Doxepin 6 mg</td> <td data-bbox="808 1283 1015 1339">Sertraline 50 mg + Doxepin Placebo</td> <td data-bbox="1015 1283 1230 1339">Sertraline 50 mg + Doxepin Placebo</td> <td data-bbox="1230 1283 1437 1339">Sertraline 50mg + Doxepin 6 mg</td> </tr> <tr> <td data-bbox="602 1339 808 1480"> <ul style="list-style-type: none"> • Doxepin PK • PD Assessments • Nordoxepin PK </td> <td data-bbox="808 1339 1015 1480"></td> <td data-bbox="1015 1339 1230 1480"> <ul style="list-style-type: none"> • Sertraline PK • PD Assessments </td> <td data-bbox="1230 1339 1437 1480"> <ul style="list-style-type: none"> • Doxepin PK • Sertraline PK • PD Assessments • Nordoxepin PK </td> </tr> </tbody> </table> <p>Doxepin lot no: 6 mg tablet 3044566 : placebo 3044565</p> <p>Sertraline HCl (Zoloft[®]) lot no: 50 mg tablets 05-0060 : placebo 05-0061</p> <p><u>Diet:</u> Subjects were required to fast overnight for at least 4 hours prior to study drug administration through 4 hours postdose. Fluids were restricted from 1 hour predose to 1 hour postdose.</p> <p>Poppy-containing food (e.g., poppy seed bagels, breads, or muffins) was not allowed during the 3 days before any urine drug screen.</p>				Treatment Period 1		Treatment Period 2		Day 1	Days 8-13	Day 14	Day 15	Sertraline Placebo + Doxepin 6 mg	Sertraline 50 mg + Doxepin Placebo	Sertraline 50 mg + Doxepin Placebo	Sertraline 50mg + Doxepin 6 mg	<ul style="list-style-type: none"> • Doxepin PK • PD Assessments • Nordoxepin PK 		<ul style="list-style-type: none"> • Sertraline PK • PD Assessments 	<ul style="list-style-type: none"> • Doxepin PK • Sertraline PK • PD Assessments • Nordoxepin PK
Treatment Period 1		Treatment Period 2																		
Day 1	Days 8-13	Day 14	Day 15																	
Sertraline Placebo + Doxepin 6 mg	Sertraline 50 mg + Doxepin Placebo	Sertraline 50 mg + Doxepin Placebo	Sertraline 50mg + Doxepin 6 mg																	
<ul style="list-style-type: none"> • Doxepin PK • PD Assessments • Nordoxepin PK 		<ul style="list-style-type: none"> • Sertraline PK • PD Assessments 	<ul style="list-style-type: none"> • Doxepin PK • Sertraline PK • PD Assessments • Nordoxepin PK 																	

	<p>Alcohol was prohibited for 48 hours before any study visit until 48 hours after dosing.</p> <p>Caffeine-containing products were prohibited for 24 hours before any study visit until 48 hours after dosing.</p>
Sampling for PK: Blood	Blood samples were collected for PK evaluation predose (0 hour) and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours postdose following administration of Treatment A and Treatment C (for doxepin and nordoxepin), and predose (0 hour) and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose following administration of Treatment B and Treatment C (for sertraline)
Measurements for PD	Measures of sedation (Digit Symbol Substitution Test [DSST], Symbol Copying Test [SCT], and Visual Analogue Scale [VAS] ratings of sleepiness) were conducted predose (0 hour), and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose following administration of Treatment A (Day 1), Treatment B (Day 14), and Treatment C (Day 15).
Analysis	<p><u>Method</u> Doxepin and nordoxepin: LC/MS/MS</p> <p><u>Lower Limits of Quantitation</u> <u>Plasma</u> Doxepin 0.05 ng/mL Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL) : ≤ 6.1% Inter-day accuracy: -2.7 to -4.7 % Long term Stability: 19 days at -70 °C</p> <p>Nordoxepin 0.05 ng/mL Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL): ≤ 4.1% Inter-day accuracy: -5.4 to -9.3 % Long term Stability: 19 days at -70 °C</p> <p>Sertraline: LC/MS/MS</p> <p><u>Lower Limits of Quantitation</u> <u>Plasma</u> Sertraline 0.1 ng/mL Inter-day Precision (%CV for Quality Controls) : ≤ 6.51 % Inter-day accuracy: -1.0 to -5.01 % Long term Stability: 1428 days at -20 °C</p>
PK Assessment	<u>Doxepin and nordoxepin</u> : AUC _{0-t} , AUC ₀₋₂₄ , AUC ₀₋₄₈ , AUC ₀₋₇₂ , AUC ₀₋₉₆ , AUC _{0-∞} , C _{max} , T _{max} , λ _z and t _{1/2} . CL/F and V _d /F were assessed for doxepin only.

	<u>Sertraline</u> : AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , C_{min} , T_{max} , and T_{min} . Sertraline steady state was assessed for trough (predose) plasma concentrations collected on Day 15 and Day 14.
PD Assessment	The primary PD analysis evaluated change from predose to postdose DSST, SCT, and VAS scores. Secondary PD analyses included calculation of the E_{max} and TE_{max} parameters using change from predose DSST, SCT, and VAS scores.
PK/PD	The PK/PD correlation was assessed by exploring the relationships between C_{max} and E_{max} and between T_{max} and TE_{max} for each treatment.
Safety Assessment	AEs, physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (serum chemistry, hematology, and urinalysis etc)

Pharmacokinetic Results:

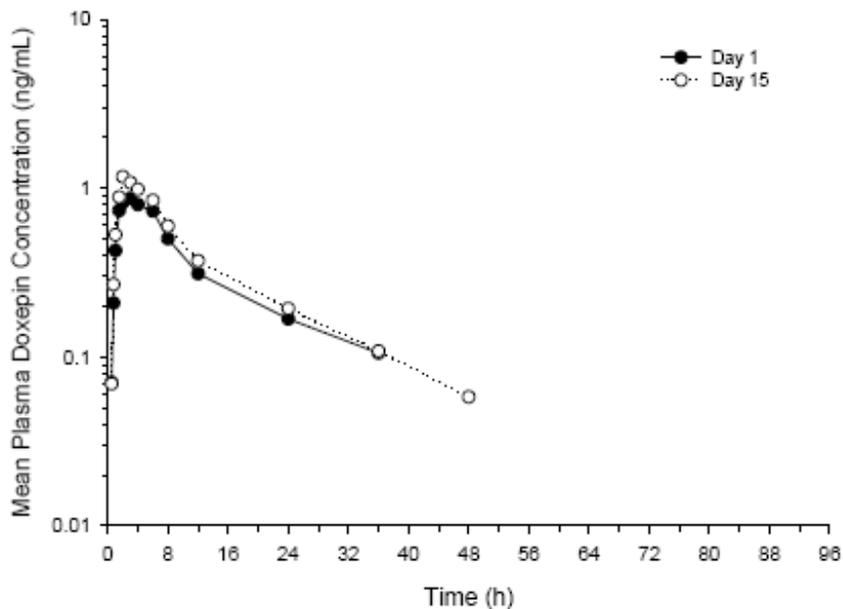
Doxepin in plasma:

Descriptive Statistics for Doxepin PK Parameters are shown in the following table:

Parameter (unit)	Treatment A (Doxepin 6 mg) N=24	Treatment C (Doxepin 6 mg + Sertraline 50 mg) N=24
AUC_{0-t} (ng*h/mL)	12.64 (106.3) n=24	14.78 (79.4) n=24
$AUC_{0-\infty}$ (ng*h/mL)	14.40 (98.0) n=23	16.29 (75.1) n=24
C_{max} (ng/mL)	0.9843 (61.7) n=24	1.270 (54.3) n=24
T_{max} (h)	3.0 (1.0–6.0) n=24	2.0 (1.5–6.0) n=24
$t_{1/2}$ (h)	14.42 (33.2) n=23	13.96 (32.2) n=24
λ_z (1/h)	0.05610 (52.8) n=23	0.05740 (50.3) n=24
CL/F (L/h)	650.2 (58.0) n=23	520.8 (53.6) n=24
Vd/F (L)	11600 (39.2) n=23	8979 (30.4) n=24

The estimates presented are arithmetic mean (CV%) for all parameters except T_{max} which is presented by median (range).

Mean doxepin concentration-time plot (with or without sertraline) for each of the treatments is shown in the following figure:



Day 1: Treatment A (doxepin 6 mg)
 Day 15: Treatment C (doxepin 6 mg + sertraline 50 mg)

Statistical Comparison of Doxepin PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	A	24	9.353	C/A	127.6	(113.4, 143.6)
	C	24	11.94			
AUC _{0-∞} (ng*h/mL)	A	23	11.14	C/A	120.5	(109.0, 133.3)
	C	24	13.43			
C _{max} (ng/mL)	A	24	0.8518	C/A	131.6	(113.8, 152.2)
	C	24	1.121			

Treatment A = Doxepin 6 mg, fasted.
 Treatment C = Doxepin 6 mg + sertraline 50 mg, fasted.

- AUC_{0-∞} and C_{max} of doxepin increased by approximately 21 % and 32 %, respectively, when co-administered with 50 mg sertraline.
- The median T_{max} was 1 hour earlier when coadministered with sertraline.
- The mean t_{1/2} was similar between two treatments with or without co-administration of sertraline.
- The 90% CIs for the ratios of the geometric LS means between Treatment C (doxepin 6 mg with sertraline 50 mg) and Treatment A (doxepin 6 mg) were above the equivalence limits of 80% to 125% for AUC_{0-t} (113.4, 143.6), AUC_{0-∞} (109.0, 133.3), and C_{max} (113.8, 152.2) indicating steady-state sertraline levels significantly affected doxepin exposure.

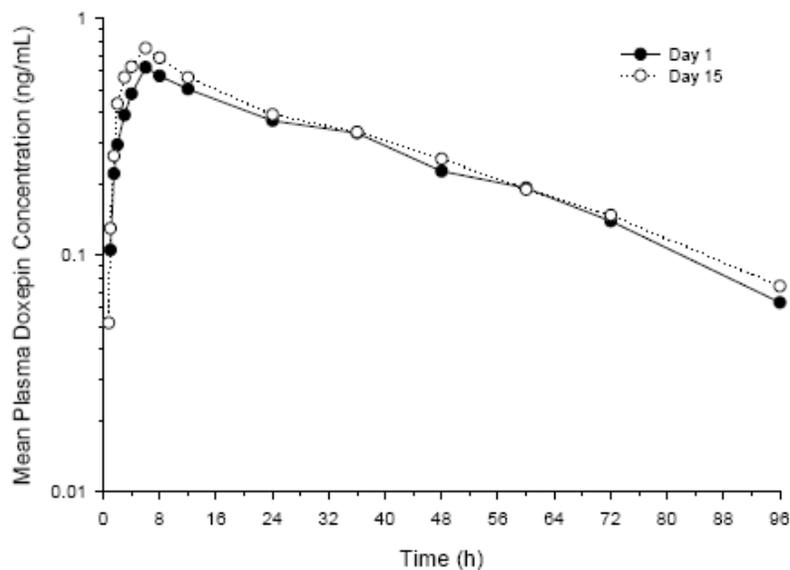
Nordoxepin in plasma:

Descriptive Statistics for Nordoxepin PK Parameters are shown in the following table:

Parameter (unit)	Treatment A (Doxepin 6 mg) N=24	Treatment C (Doxepin 6 mg + Sertraline 50 mg) N=24
AUC _{0-t} (ng*h/mL)	24.56 (46.2) n=24	27.08 (49.3) n=24
AUC _{0-∞} (ng*h/mL)	28.70 (49.5) n=24	28.78 (40.0) n=23
C _{max} (ng/mL)	0.6305 (25.4) n=24	0.7788 (28.4) n=24
T _{max} (h)	6.0 (2.0–12.0) n=24	6.0 (2.0–8.0) n=24
t _{1/2} (h)	28.71 (16.5) n=24	29.18 (29.0) n=24

The estimates presented are arithmetic mean (CV%) for all parameters except T_{max} which is presented by median (range).

Mean nordoxepin concentration-time plot for each of the treatments is shown in the following figure:



Day 1: Treatment A (doxepin 6 mg)
Day 15: Treatment C (doxepin 6 mg + sertraline 50 mg)

Statistical Comparison of Nordoxepin PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	A	24	22.78	C/A	109.0	(101.8, 116.8)
	C	24	24.84			
AUC _{0-∞} (ng*h/mL)	A	24	26.51	C/A	106.7	(100.3, 113.5)
	C	23	28.28			
C _{max} (ng/mL)	A	24	0.6124	C/A	122.5	(114.9, 130.7)
	C	24	0.7502			

Treatment A = Doxepin 6 mg, fasted.

Treatment C = Doxepin 6 mg + sertraline 50 mg, fasted.

- Nordoxepin C_{max} was slightly higher (~23%) when doxepine was co-administered with 50 mg sertraline.
- The median T_{max}, 6 hours postdose, was not altered between two treatments with or without co-administration of sertraline.
- The mean t_{1/2} was similar between two treatments with or without co-administration of sertraline.
- The 90% CIs for the ratios of the geometric LS means between Treatment C (doxepin 6 mg with sertraline 50 mg) and Treatment A (doxepin 6 mg) were completely contained within the equivalence limits of 80% to 125% for AUC_{0-t} (101.8, 116.8) and AUC_{0-∞} (100.3, 113.5) whereas the C_{max} (114.9, 130.7) is above the equivalence limits.

Sertraline in plasma:

Descriptive Statistics for Sertraline PK Parameters are shown in the following table:

Parameter (unit)	Treatment B (Sertraline 50 mg) N=24	Treatment C (Doxepin 6 mg + Sertraline 50 mg) N=24
AUC _{0-t} (ng*h/mL)	281.4 (37.4) n=24	301.8 (45.4) n=24
AUC _{0-τ} (ng*h/mL)	281.4 (37.4) n=24	301.8 (45.4) n=24
C _{min} (ng/mL)	7.934 (44.5) n=24	7.807 (45.9) n=24
C _{max} (ng/mL)	17.24 (32.7) n=24	18.77 (42.7) n=24
T _{min} (h)	0.750 (0.170–23.5) n=24	0.5 (0.0–24.0) n=24
T _{max} (h)	6.0 (3.0–8.0) n=24	6.0 (6.0–8.0) n=24

The estimates presented are arithmetic mean (CV%) for all parameters except T_{max} and T_{min} which are presented by median (range).

Statistical Comparison of Sertraline PK Parameters:

Parameter (unit)	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL)	B	24	263.6	C/B	104.9	(100.4, 109.6)
	C	24	276.5			
AUC _{0-τ} (ng*h/mL)	B	24	263.6	C/B	104.9	(100.4, 109.6)
	C	24	276.5			
C _{max} (ng/mL)	B	24	16.37	C/B	105.6	(98.4, 113.3)
	C	24	17.29			

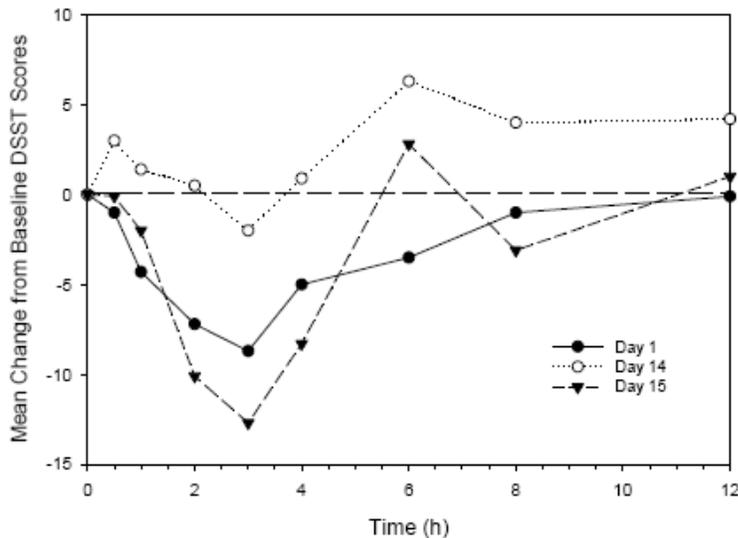
Treatment B = Sertraline 50 mg, fasted.

Treatment C = Doxepin 6 mg + sertraline 50 mg, fasted.

- Sertraline steady-state did not increase significantly (5 %) when doxepine was co-administered with sertraline.
- The median T_{max}, 6 hours postdose, was not altered between two treatments with or without co-administration of doxepine.
- The 90% CIs for the ratios of the geometric LS means between Treatment C (doxepin 6 mg with sertraline 50 mg) and Treatment B (sertraline 50 mg) were completely contained within the equivalence limits of 80% to 125% for AUC_{0-τ} (100.4, 109.6) and C_{max} (98.4, 113.3) indicating doxepin did not significantly affect sertraline exposure.

Pharmacodynamic Results:

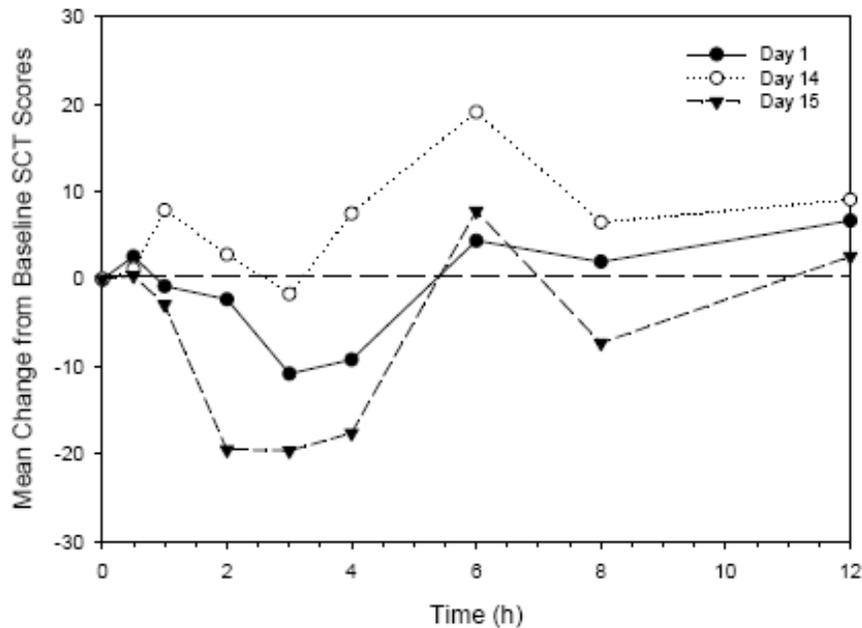
Digit Symbol Substitution Test (DSST): Decreases below 0 = increases sedation



Day 1: Treatment A (doxepin 6 mg)
 Day 14: Treatment B (sertraline 50 mg)
 Day 15: Treatment C (doxepin 6 mg + sertraline 50 mg)

- The initial increases in in sedation (based on mean DSST scores) were observed 0.5 hour and 1 hour postdose following administration of doxepin alone and coadministration of doxepin with sertraline, respectively.
- The greatest reduction in DSST scores was reached at 3 hours postdose of doxepin administration with or without sertraline.
- The greatest relative decrease occurred following coadministration of doxepin with sertraline.
- The DSST scores returned to approximately predose values by 6 hours postdose following coadministration of doxepin with sertraline and and 8 hours following administration of doxepin alone, respectively.
- The maximum decreases in mean DSST scores were not significantly different between treatments of doxepin with or without coadministration of sertraline.

Symbol Copying Test (SCT): Decreases below 0 = decreases motor speed

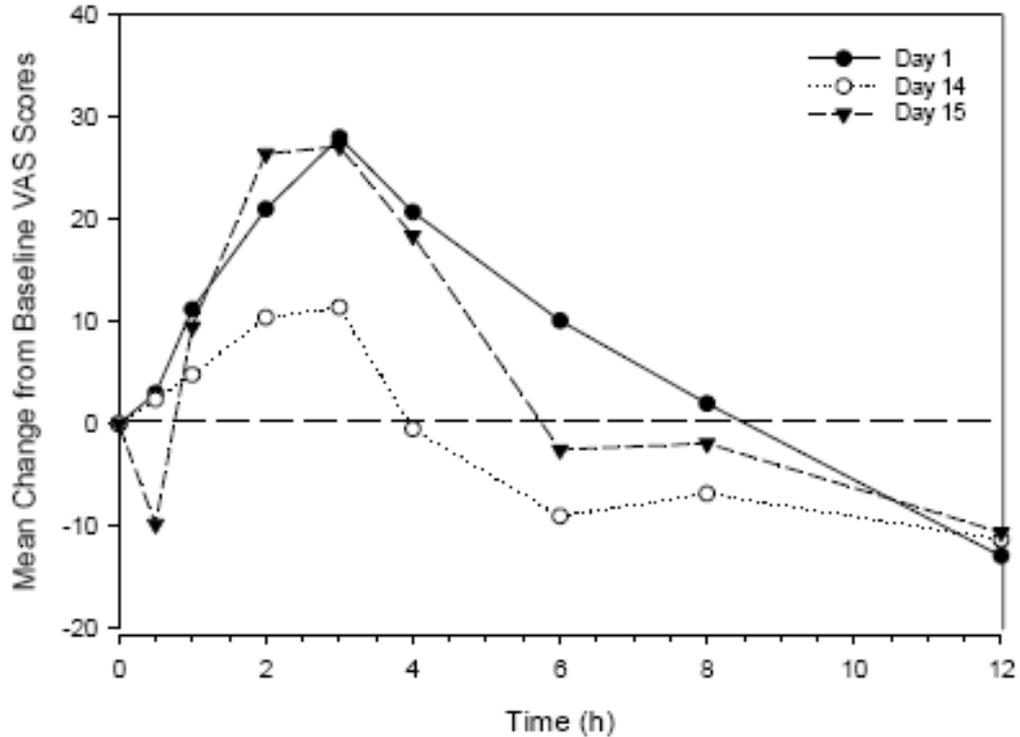


Day 1: Treatment A (doxepin 6 mg)
 Day 14: Treatment B (sertraline 50 mg)
 Day 15: Treatment C (doxepin 6 mg + sertraline 50 mg)

- The initial decreases in motor speed (based on mean SCT scores) were observed 1 hour postdose following administration of doxepin with or without sertraline.
- The greatest reduction in SCT scores occurred approximately 2–3 hours postdose following administration of doxepin with or without sertraline.
- The greatest relative decrease occurred following coadministration of doxepin with sertraline.
- The SCT scores returned to predose levels by approximately 6 hours postdose following administration of doxepin with or without sertraline.

- Maximum decreases in mean SCT scores were significantly greater following coadministration of doxepin with sertraline when compared with doxepin alone.

Visual Analogue Scale (VAS)

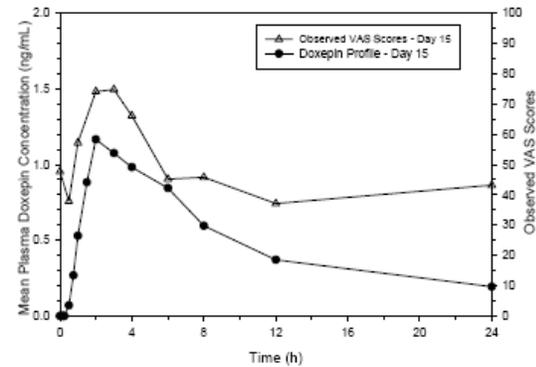
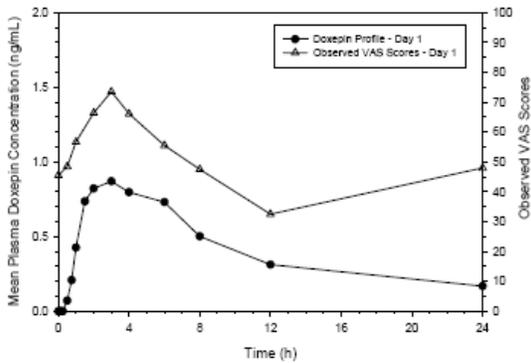
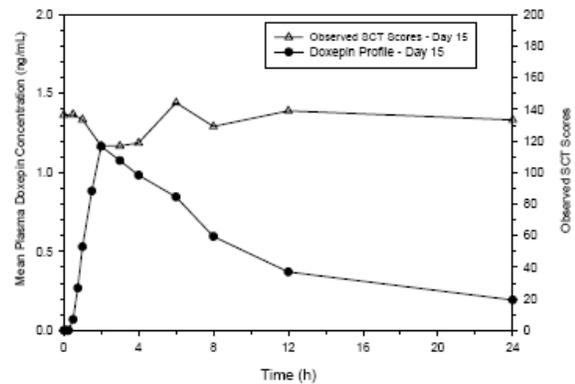
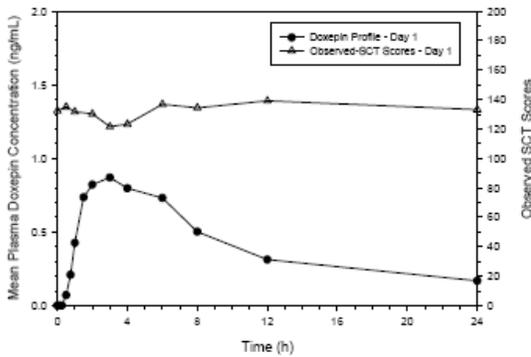
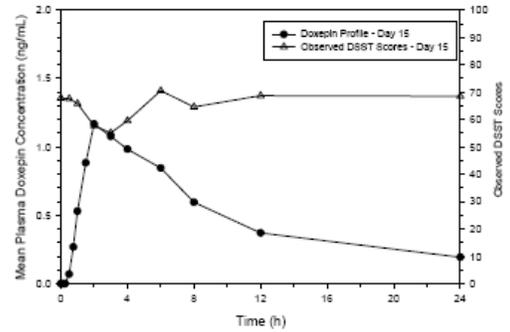
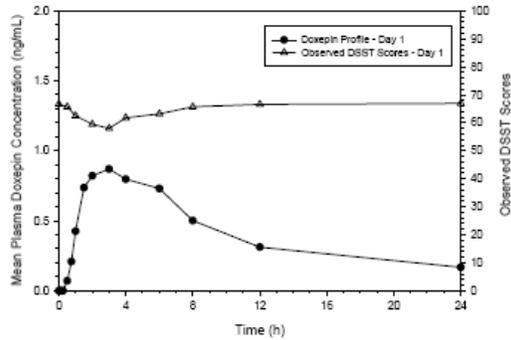


Increases above 0 = sleepiness; decreases below 0 = alertness

Day 1: Treatment A (doxepin 6 mg)
 Day 14: Treatment B (sertraline 50 mg)
 Day 15: Treatment C (doxepin 6 mg + sertraline 50 mg)

- The initial increases in subjective ratings of sleepiness (based on mean VAS scores) were observed 1 hour and 0.5 hour postdose following coadministration of doxepin with sertraline and administration of doxepin alone, respectively.
- The VAS scores reached their greatest increase at 3 hours postdose following administration of doxepin with or without sertraline.
- The VAS scores returned to approximately predose levels at 6 hours and 8 hours postdose following coadministration of doxepin with sertraline and administration of doxepin alone, respectively.
- The maximum increases in mean VAS scores were not significantly different following coadministration of doxepin with sertraline when compared with doxepin alone.

PK/PD Results:



- A trend was evident between increased plasma concentrations and increased sedation (based on DSST, SCT, and VAS scores) following administration of doxepin with or without sertraline, however, the correlations were not statistically significant.
- The greatest increases in sedation, based on mean DSST, SCT, and VAS scores, occurred at or near the doxepin estimated median T_{max} following administration of doxepin with or without sertraline.
- The mean change from baseline was similar following administration of doxepin with or without sertraline.
- These scores returned to approximately baseline at 6–8 hours postdose despite residual plasma concentrations.

Conclusions:

- A drug interaction was observed when doxepin was coadministered with sertraline. AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} estimates of doxepin were approximately 28%, 21%, and 32% higher, respectively, in the sertraline coadministration treatment group.
- Nordoxepin exposure was not affected by coadministration of doxepin with sertraline.
- A slightly increase of sertraline concentrations (5%) in AUC and C_{max} were observed but not statistically significant indicating sertraline exposure was not affected by co-administration of doxepin.
- Maximum increase in sedation based on mean DSST and SCT scores was observed. Sedation was slightly more pronounced following coadministration of doxepin with sertraline than doxepin alone.
- Increases in subjective ratings of sleepiness based on mean VAS scores were comparable following administration of doxepin with or without sertraline.
- The greatest increases in sedation occurred approximately 3 hours postdose (near doxepin T_{max}) following administration of doxepin with or without sertraline.
- Although not statistically significant, a trend was evident between increased doxepin plasma concentrations and increased sedation following administration of doxepin with or without sertraline.
- The mean change from baseline DSST, SCT, and VAS scores was similar between the two groups. These scores returned to approximately baseline at 6–8 hours postdose despite residual plasma concentrations.

Study SP-0507: A Randomized, Open-Label Study to Assess the Relative Bioavailability of Silenor™ (Doxepin HCl) 6 mg Tablets Compared to Sinequan® (Doxepin HCl) 50 mg Capsules

A brief overview of some essential components of the study design is given below:

Study Design	Single-dose, randomized, open-label, two-way crossover						
Study Population	N=24 <u>Age:</u> 18-42 years (mean 26.5 years) <u>Gender:</u> 24 males and females (19M/5F) <u>Weight:</u> 55-120.5 kg (mean 84.48 kg) <u>Race:</u> White (91.7%) and African American (8.3%)						
Dosage and Administration	Subjects were randomized to 6 mg tablet (A) or 50 mg capsule (B) in a treatment sequence (A/B or B/A). Drugs were administered under fasted condition. There was a 9-day washout period between Treatment periods. Doxepin Lot no: 6 mg tablet 3044566 Sinequan® (Doxepin HCl) Lot no: 50 mg capsules 0262K03A <u>Diet:</u> Subjects were fasted overnight for at least 10 hours prior to study drug administration through 4 hours postdose. Fluids were restricted from 1 hour predose to 1 hour postdose. Poppy-containing food (e.g., poppy seed bagels, breads, or muffins) was not allowed during the 3 days before any urine drug screen. Alcohol was prohibited for 48 hours before any study visit until 48 hours after dosing. Caffeine-containing products were prohibited for 24 hours before any study visit until 48 hours after dosing.						
Sampling: Blood	At predose (0 hour), and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours postdose. The samples were analyzed for plasma concentrations of doxepin and nordoxepin.						
Analysis	<u>Method</u> LC/MS/MS <u>Lower Limits of Quantitation</u> <table style="margin-left: 40px;"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> </tr> <tr> <td>Doxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> <tr> <td>Nordoxepin</td> <td style="text-align: center;">0.05 ng/mL</td> </tr> </table> <u>Doxepin:</u> Linear range : 0.05-10.0 ng/mL in plasma		<u>Plasma</u>	Doxepin	0.05 ng/mL	Nordoxepin	0.05 ng/mL
	<u>Plasma</u>						
Doxepin	0.05 ng/mL						
Nordoxepin	0.05 ng/mL						

	<p>Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL) : ≤ 6.1% Inter-day accuracy: -2.7 to -4.7 % Long term Stability: 19 days at -70 °C</p> <p><u>Nordoxepin:</u> Linear range : 0.05-10.0 ng/mL in plasma Inter-day Precision (%CV for Quality Controls: 0.15, 1.00, 8.00 ng/mL): ≤ 4.1% Inter-day accuracy: -5.4 to -9.3 % Long term Stability: 19 days at -70 °C</p>
PK Assessment	AUC _{0-∞} , AUC _{ext} , AUC _{0-t} , AUC ₀₋₂₄ , AUC ₀₋₄₈ , λz, C _{max} , T _{max} , t _{1/2} . CL/F and Vd/F were estimated for doxepin only.
Safety Assessment	AEs, physical examinations, vital sign measurements (blood pressure, pulse rate, respiratory rate, and temperature), serum chemistry, hematology, urinalysis and 12-lead ECG

Pharmacokinetic Results:

Doxepin in plasma:

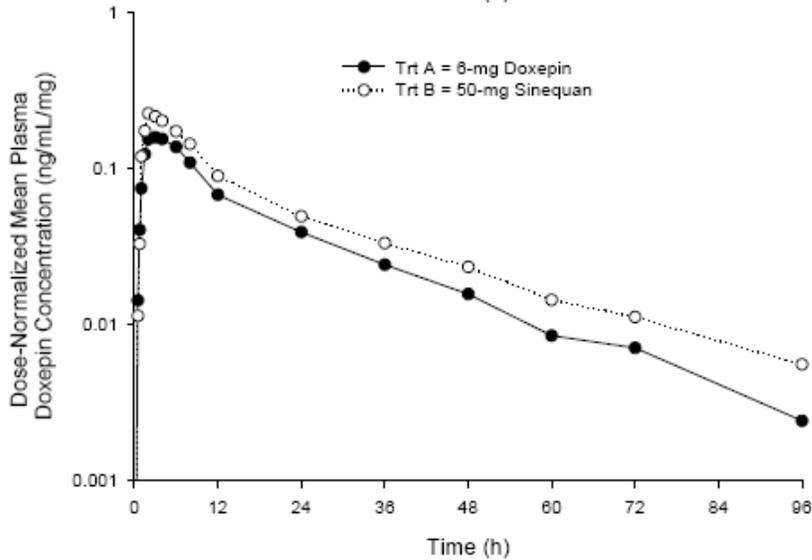
Descriptive Statistics for Dose Normalized Doxepin PK Parameters are shown in the following table:

Parameter (Unit)	Treatment A (Doxepin 6 mg tablet) N=23	Treatment B (Sinequan® 50 mg capsule) N=24
AUC _{0-t} (ng*h/mL/mg) ¹	2.816 (90.8)	3.933 (83.2)
AUC _{0-∞} (ng*h/mL/mg) ¹	3.139 (89.2)	4.148 (87.4)
C _{max} (ng/mL/mg) ¹	0.1823 (84.2)	0.2491 (90.3)
T _{max} (h)	3.0 (1.0–6.0)	2.5 (1.0–6.0)
t _{1/2} (h)	16.01 (47.7)	19.13 (28.4)
λz (1/h)	0.05372 (49.7)	0.03898 (28.7)
CL/F (L/h)	618.2 (85.6)	411.8 (73.8)
Vd/F (L)	10550 (48.4)	9821 (51.6)

¹ Derived from dose-normalized plasma concentrations.

The data presented are arithmetic mean (CV%) for all parameters except T_{max} which is presented by median (range).

Dose-Normalized Doxepin Plasma Concentration-Time Profiles:



- The median Tmax was 30 minutes delayed following administration of a 6 mg tablet (3.0 hours) compared to Sinequan 50 mg capsule (2.5 hours), although the ranges overlap (1-6 hours).
- The mean t1/2 following administration of a 6 mg tablet was approximately 3 hours short (16.01 hours) compared to Sinequan 50 mg capsule (19.13 hours).
- Mean Cmax and AUC (derived from dose-normalized plasma concentrations) were approximately 27% and 30% lower, respectively, following administration of doxepin 6 mg when compared with Sinequan 50 mg.
- The mean CL/F of doxepin 6 mg (618.2 L/h) was greater than that of Sinequan 50 mg (411.8 L/h).

Statistical Comparison of Dose-normalized Plasma Concentrations for Doxepin PK Parameters

Parameter	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL/mg)	A	23	1.939	A/B	64.5	(57.5, 72.4)
	B	24	3.006			
AUC _{0-∞} (ng*h/mL/mg)	A	23	2.222	A/B	71.4	(64.1, 79.5)
	B	24	3.114			
C _{max} (ng/mL/mg)	A	23	0.1397	A/B	73.1	(64.4, 83.0)
	B	24	0.1910			

Treatment A= doxepin 6 mg tablet, fasted; Treatment B= Sinequan[®] 50 mg capsule, fasted.

- The 90% CIs for the ratios of the geometric LS means between Treatment A (doxepin 6 mg) and Treatment B (Sinequan[®] 50 mg) for AUC_{0-t} (57.5, 72.4), AUC_{0-∞} (64.1, 79.5), and Cmax (64.4, 83.0) were not contained within the equivalence limits of 80% to 125%.

Metabolite in plasma (Nordoxepin):

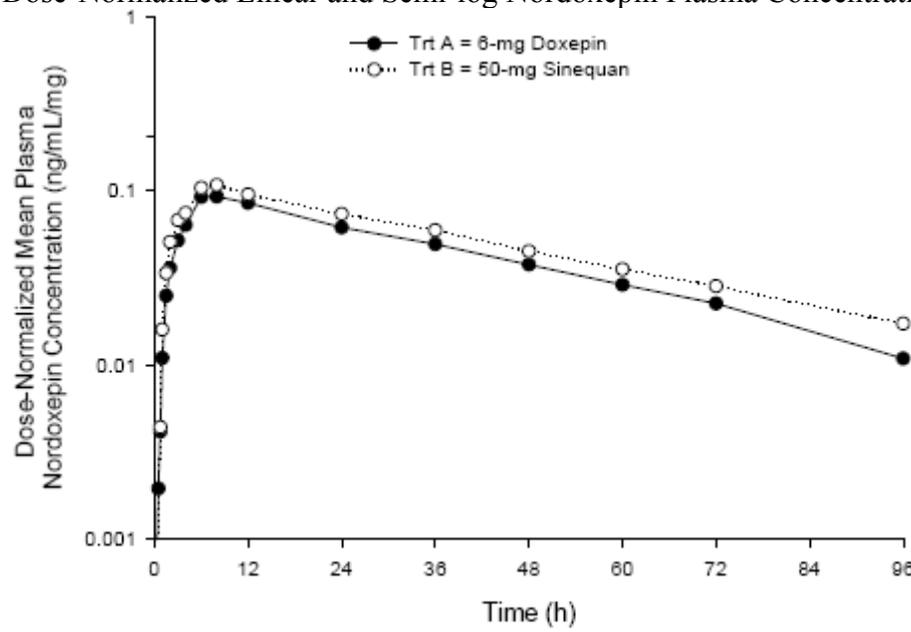
Descriptive Statistics for Dose Normalized Nordoxepin PK Parameters are shown in the following table:

Parameter (Unit)	Treatment A (Doxepin 6 mg tablet) N=23	Treatment B (Sinequan® 50 mg capsule) N=24
AUC _{0-t} (ng*h/mL/mg) ¹	3.898 (50.8) n=20	4.784 (52.5) n=24
AUC _{0-∞} (ng*h/mL/mg) ¹	4.248 (42.8) n=19	5.172 (53.5) n=23
C _{max} (ng/mL/mg) ¹	0.09656 (34.3) n=20	0.1110 (38.7) n=24
T _{max} (h)	8.0 (6.0–60.0) n=20	8.0 (6.0–36.0) n=24
t _{1/2} (h)	27.94 (31.2) n=19	28.87 (25.5) n=23
λ _z (1/h)	0.02669 (25.2) n=19	0.02553 (25.4) n=23

¹ Derived from dose-normalized plasma concentrations.

The data presented are arithmetic mean (CV%) for all PK parameters except T_{max} which is presented by median (range).

Dose-Normalized Linear and Semi-log Nordoxepin Plasma Concentration-Time Profiles:



- The median Tmax was 8.0 hours following administration of both treatments.
- The mean t_{1/2} was similar between the two treatment groups.
- The nordoxepin C_{max} and AUC (derived from dose-normalized plasma concentrations) were slightly lower (5-10%) following administration of doxepin 6 mg when compared with Sinequan 50 mg.

Statistical Comparison of Dose-normalized Plasma Concentrations for Nordoxepin PK Parameters

Parameter	Treatment	N	Geometric LS Mean	Pairwise Comparisons		
				Pair	Ratio (%)	90% CI
AUC _{0-t} (ng*h/mL/mg)	A	20	3.825	A/B	89.9	(85.4, 94.6)
	B	24	4.256			
AUC _{0-∞} (ng*h/mL/mg)	A	19	4.320	A/B	94.6	(89.9, 99.6)
	B	23	4.566			
C _{max} (ng/mL/mg)	A	20	0.09883	A/B	95.5	(90.7, 100.4)
	B	24	0.1035			

Treatment A= doxepin 6 mg tablet, fasted; Treatment B= Sinequan[®] 50 mg capsule, fasted.

- The 90% CIs for the ratios of the geometric LS means between Treatment A (doxepin 6 mg) and Treatment B (Sinequan 50 mg) for AUC_{0-t} (85.5, 94.6), AUC_{0-∞} (89.9, 99.6), and C_{max} (90.7, 100.4) were completely contained within the equivalence limits of 80% to 125%.

Conclusions:

- The relative bioavailability of doxepin between 6 mg tablets and 50 mg capsule evaluated by dose-normalized parameters showed that the C_{max} and AUC were modestly lower (approximately 27% and 30%, respectively) in 6 mg tablets when compared with 50 mg Sinequan capsules.
- Median Tmax were 30 minutes delayed although ranges were similar and t_{1/2} were approximately 3 hours shorter following 6 mg tablet administration.
- The PK profiles of nordoxepin were similar in both formulations.

Reviewer's Comment:

- *The linearity of doxepin PK within 6 to 50 mg was not known. The approach of dose normalization is therefore based on the assumption of linear PK between the evaluated dosage ranges.*
- *Although 6 mg tablet is not bioequivalent to 50 mg Sinequine capsule, the purpose of this study was to compare the relative bioavailability of the to-be-marketed product to the already marketed product; therefore the bioequivalence is not required.*

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Molecular Weight 315.84

White, crystalline powder

pKa: not given

Classification: Based on the following information on solubility, permeability and dissolution, doxepin can not be classified as a BCS Class I drug due to the lack of information required for classification (Please refer to the Guidance: Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System).

SOLUBILITY:

There is very limited solubility information of doxepin provided by the sponsor. Below is the only data described in the submission.

The intrinsic solubility of doxepin HCl, USP was potentiometrically determined using a ^{(b) (4)} titration methodology. All experiments were titrated from low to high pH and precipitate was observed. The observed solubility ranged from 649 mg/250 mL at pH=7.5 to 19 mg/250 mL at pH=11.9. According to Henderson-Hasselbach theory, when the potentiometrically-generated solubility data are plotted in the range of pH 1 to 7.5, doxepin HCl, USP clearly demonstrates solubility values consistent with a Class 1 molecule as defined in the Biopharmaceutics Classification System (BCS). No data was provided.

Reviewer's comments:

- The base titration method was utilized. This is acceptable according to the guidance; however, no justification for the use of this method was provided by the sponsor.
- Other deficiencies also include: lack of pKa information, the solubility within pH range of 1 to 7.5.

PERMEABILITY:

Permeability of doxepin HCl was evaluated using an in vitro monolayer model, the Caco-2 human colonic-derived cell line.

The permeability studies were conducted at ^{(b) (4)}

Cell Culture:

^{(b) (4)}

(b) (4)

Permeability Methods:

(b) (4)





Conclusions:

- The average Papp value for Doxepin Hydrochloride is greater than the Papp value of pindolol at all three concentrations.
- The B-to-A Papp to A-to-B Papp ratios of Doxepin Hydrochloride are less than 3 at all three concentrations. This is evidence that Doxepin Hydrochloride permeates the Caco-2 membrane by passive diffusion.

Reviewer's comments:

- The sponsor has selected pindolol and atenolol as high and low P markers. However, the suitability of the method was not established based on selected 20 model drugs along with data on their extent of absorption in humans and a plot of the extent of absorption on a function of permeability was not provided.

DISSOLUTION:

The solubility studies were conducted at

(b) (4)

Dissolution Method:

Development work employed USP <711> Apparatus 1 to determine the dissolution values of capsules and USP <711> Apparatus 2 to determine the dissolution values of the tablets. Various dissolution media were studied including simulated gastric fluid without

enzymes (pH=1.2), a 0.05 M acetate buffer (pH=4.5) and simulated intestinal fluid (pH=6.8).

Apparatus:	USP II (Paddles) for Doxepin HCl tablets
	USP I (Baskets) for Doxepin HCl capsules
Shaft Rotation:	50 RPM
Dissolution Fluid:	Simulated Gastric Fluid, without enzymes
Volume:	900 mL
Temperature:	37.0 ± 0.5 °C
Sampling Times:	5, 8, 12, 15, and 30 minutes
Aliquot Volume:	10 mL
Fluid Replacement:	None

Results:

Rapid dissolution occurred for both dosage forms with mean doxepin concentrations of greater than ^{(b) (4)} achieved in 30 minutes for all samples tested.

Figure 3.2.P.2.2.1-2 and Figure 3.2.P.2.2.1-3 present the comparative dissolution profiles of the capsule and tablet formulations (1 mg and 6 mg) in simulated gastric fluid without enzymes (pH=1.2). Similar dissolution profiles were obtained for the capsule and tablets as indicated by f2 (similarity factor) values of 61.3 and 57.2, for the 1 mg and 6 mg strengths respectively. The Silenor tablets are rapidly dissolved and no difference was seen between the capsule and tablet formulations.

Conclusion: More than (b) (4) is dissolved by 15 minutes. Hence, doxepin tablets can be considered “rapidly dissolving”.

Overall Conclusion: The BCS classification could not be established due to incomplete information provided in this submission.

Study SP-D0115: Binding of Doxepin to Human, Rat, Rabbit, and Mouse Plasma Proteins Using Equilibrium Dialysis-Based Method

This plasma protein binding study was performed by (b) (4)

Method:

STUDY DESIGN SUMMARY

Assay(s): Plasma protein binding (equilibrium dialysis; incl. plasma and buffer recovery)

Test articles: 1; doxepin

Test concentration(s): 2 µM

Specie(s): Human, rat, rabbit, and mouse

Time point(s): ~20 h

Replicates: n=2

Dependent studies/projects (if any): N/A

Materials: Pooled heparinized human, rat, rabbit, and mouse plasma will be obtained from (b) (4) or similar. Plasma will be centrifuged at approx. (b) (4)

Apparatus: Teflon 96-well dialysis plate (HTDialysis) with 12-14K MWCO regenerated cellulose membrane (e.g., Spectrapor). Teflon 96-well microtiter plate (e.g., Spike International) used for recovery/stability assessment.

Experimental method:

Plasma protein concentration: ~99.9% plasma final

Buffer: 70 mM NaCl, 50 mM Na phosphate, pH 7.4

DMSO concentration: ≤1.0% final

Incubation temperature: 37±2°C

Matrix matching: plasma samples will be matrix-matched 1:1 with buffer, and buffer samples will be matrix-matched 1:1 with plasma.

Rapid equilibration check using comparison of % bound in both vectors (plasma-to-buffer and buffer-to-plasma).

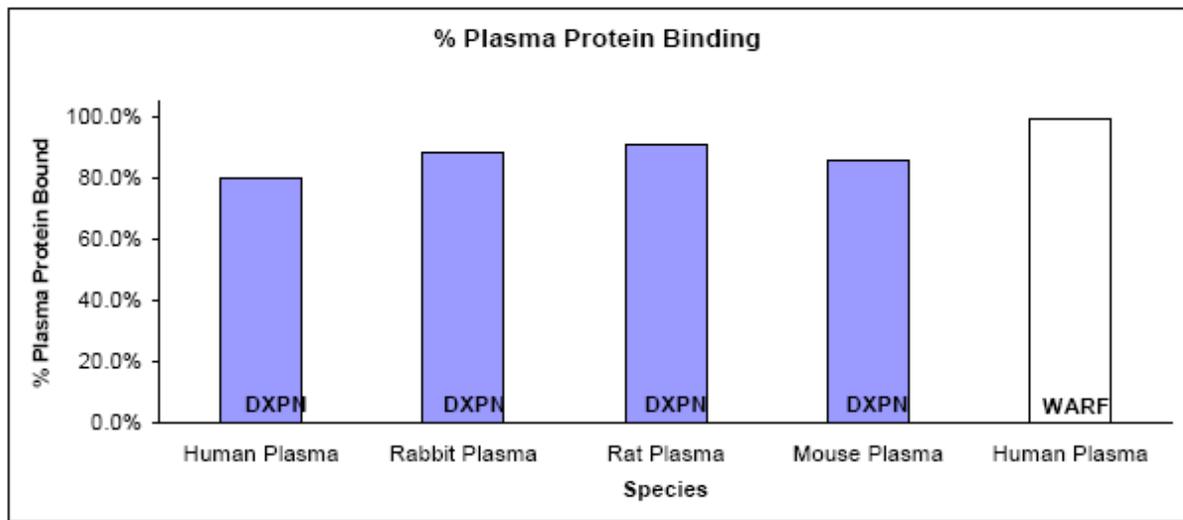
Plasma and buffer recovery assessments in both the Teflon dialysis apparatus and Teflon microtiter plate: 20hr, 37±2°C, in parallel with the dialysis procedure.

Results: A summary of the binding results for all species was given below.

Plasma Protein Binding Results Summary (Equilibrium Dialysis)

Test Compound	Matrix Species	% Plasma Protein Bound (Plasma-to-Buffer)	Equilibrium Ratio (Plasma-to-Plasma) *	% Recovery on Assay Plate (Plasma-to-Buffer)	Comment
Doxepin	Human Plasma	80.3%	0.99	79.3%	DXPN
Doxepin	Rabbit Plasma	88.5%	1.04	83.7%	DXPN
Doxepin	Rat Plasma	90.8%	1.32	72.6%	DXPN
Doxepin	Mouse Plasma	86.0%	1.02	73.0%	DXPN
Warfarin	Human Plasma	99.2%	3.95	78.7%	WARF

* ER = 1 if equilibrium is achieved



- Over all, the protein binding is 80.3-90.8% and the recovery is 72.6-83.7% throughout different species.
- Human plasma protein binding of doxepin (80.3%) is 6-10% lower than other species tested.
- The dialysis was at or near equilibrium in all species.
- There is 99.2% human plasma protein binding in warfarin with 78.7% recovered, however, the equilibrium was not achieved.

Below is the individual data for human plasma tested (data for other species were not listed in this review):

(b) (4)



- Only 2 replications were performed and therefore not able to evaluate the variations, however, the individual data seemed to be consistent though.

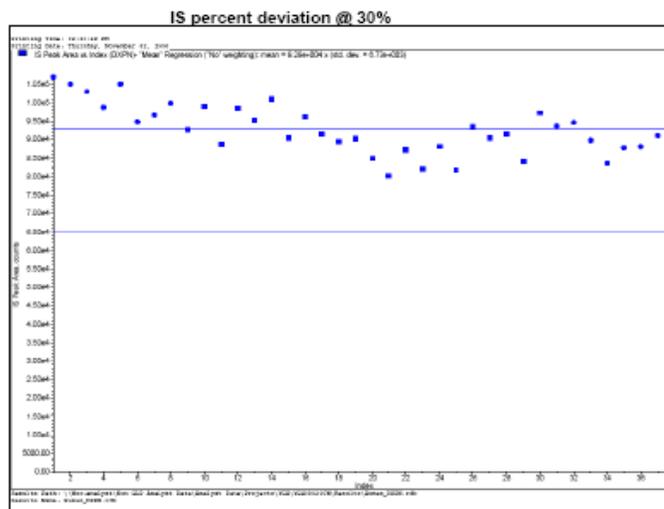
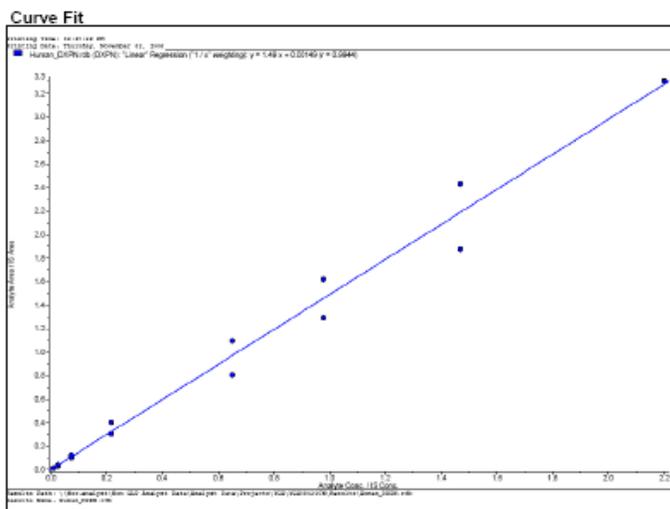
Below are the analytical data for calibration curve and residues for IS peak area:

SUMMARY OF CALIBRATION STANDARD BACK-CALCULATED CONCENTRATION IN PLASMA

	Calibration Standard Nominal Theoretical Concentrations (µM)							
Replicate 1	0.0080	0.024	0.072	0.22	0.66	0.88	1.47	2.2
Replicate 2	0.0071	0.020	0.067	0.21	0.54	0.87	1.26	2.2
Mean	0.0076	0.023	0.074	0.21	0.64	0.98	1.45	2.2
%Bias	-5.8	-3.9	2.7	-5.7	-2.1	0.1	-1.5	0.9
n	2	2	2	2	2	2	2	2

Best Available Copy

Calibration Parameters:
 Type Linear
 Weighting 1/X
 R² 0.9944
 LOQ (µM) 0.0080



- The residue plot for IS peak area exhibits slight downward trend initially but the trend diminished for most part of the plot and the deviation was within 30%.

Conclusion:

The protein binding of doxepin to human plasma is approximately 80% while other tested species showed 6-10% higher binding.

Study SP-D0118:

CYP Inhibition Study of Doxepin HCl

This in vitro CYP Inhibition study was performed by [REDACTED] ^{(b) (4)}

Method: Below is a list of reference compounds used for comparison of the study results.

Assay	Source	Reference Compound	Bibliography
CYP1A2 Inhibition (recombinant, CEC substrate)	Human recombinant (1.25 pmol/mL)	furafylline	Crespi et al. (1997)
CYP2B6 Inhibition (recombinant, EFC substrate)	Human recombinant (10 pmol/mL)	ketoconazole	Ekins et al. (1997)
CYP2C8 Inhibition (recombinant, DBF substrate)	Human recombinant (20 pmol/mL)	quercetin	Miller et al. (2000)
CYP2C9 Inhibition (recombinant, MFC substrate)	Human recombinant (15 pmol/mL)	sulfaphenazole	Crespi et al. (1997)
CYP2C19 Inhibition (recombinant, CEC substrate)	Human recombinant (10 pmol/mL)	tranylcypromine	Ono et al. (1996)
CYP2D6 Inhibition (recombinant, MFC substrate)	Human recombinant (50 pmol/mL)	quinidine	Ono et al. (1996)
CYP2E1 Inhibition (recombinant, EC substrate)	Human recombinant (15 pmol/mL)	4-methylpyrazole	Yamazaki et al. (1996)
CYP1A2 Inhibition (recombinant, phenacetin substrate)	Human recombinant (5 pmol/mL)	furafylline	Weaver et al. (2003)
CYP2C9 Inhibition (recombinant, diclofenac substrate)	Human recombinant (40 pmol/mL)	sulfaphenazole	Dierks et al. (2001)
CYP2C19 Inhibition (recombinant, omeprazole substrate)	Human recombinant (1 pmol/mL)	tranylcypromine	Zhang W et al. (2001)
CYP2D6 Inhibition (recombinant, dextromethorphan substrate)	Human recombinant (15 pmol/mL)	quinidine	Vengurlekar et al. (2002)
CYP3A4 Inhibition (recombinant, testosterone substrate)	Human recombinant (22 pmol/mL)	ketoconazole	Lin et al. (2001)
CYP3A4 Inhibition (recombinant, midazolam substrate)	Human recombinant (20 pmol/mL)	ketoconazole	Gorski et al. (1994)

Below are the experimental conditions:

Assay	Substrate / Cofactor	Incubation	Detected Component	Analytical Method
CYP1A2 Inhibition (recombinant, CEC substrate)	Test compound (10 μ M) CEC (5 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 30 min, 37 $^{\circ}$ C	CHC	Fluorimetry
CYP2B6 Inhibition (recombinant, EFC substrate)	Test compound (10 μ M) EFC (1.5 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 50 min, 37 $^{\circ}$ C	HFC	Fluorimetry
CYP2C8 Inhibition (recombinant, DBF substrate)	Test compound (10 μ M) DBF (0.25 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 90 min, 37 $^{\circ}$ C	fluorescein	Fluorimetry
CYP2C9 Inhibition (recombinant, MFC substrate)	Test compound (10 μ M) MFC (50 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 80 min, 37 $^{\circ}$ C	HFC	Fluorimetry
CYP2C19 Inhibition (recombinant, CEC substrate)	Test compound (10 μ M) CEC (25 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 60 min, 37 $^{\circ}$ C	CHC	Fluorimetry
CYP2D6 Inhibition (recombinant, MFC substrate)	Test compound (10 μ M) MFC (50 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 60 min, 37 $^{\circ}$ C	HFC	Fluorimetry
CYP2E1 Inhibition (recombinant, EC substrate)	Test compound (10 μ M) EC (4 μ M), NADP (8.2 μ M), G6P (3.3 mM), G6PDHase (0.4 U/mL) BSA (0.4 mg/mL) (n=2)	0 and 50 min, 37 $^{\circ}$ C	HC	Fluorimetry

CYP1A2 Inhibition (recombinant, phenacetin substrate)	Test compound (10 μ M), Phenacetin (10 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL)	15 min, 37°C	acetaminophen	HPLC-MS/MS
CYP2C9 Inhibition (recombinant, diclofenac substrate)	Test compound (10 μ M) Diclofenac (10 μ M), NADP (0.52 mM), G6P (1.32 mM), G6PDHase (0.16 U/mL) (n=2)	30 min, 37 °C	4'-hydroxydiclofenac	HPLC-MS/MS
CYP2C19 Inhibition (recombinant, omeprazole substrate)	Test compound (10 μ M) Omeprazole (0.5 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) (n=2)	30 min, 37°C	5-hydroxyomeprazole	HPLC-MS/MS
CYP2D6 Inhibition (recombinant, dextromethorphan substrate)	Test compound (10 μ M) Dextromethorphan (5 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) (n=2)	20 min, 37 °C	Dextrorphan	HPLC-MS/MS
CYP3A4 Inhibition (recombinant, testosterone substrate)	Test compound (10 μ M) Testosterone (50 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) (n=2)	15 min, 37°C	6 β -hydroxytestosterone	HPLC-MS/MS
CYP3A4 Inhibition (recombinant, midazolam substrate)	Test compound (10 μ M) Midazolam (5 μ M), NADP (1.3 mM), G6P (3.3 mM), G6PDHase (0.4 U/mL) (n=2)	20 min, 37°C	1-hydroxymidazolam	HPLC-MS/MS

The percentage inhibition was calculated by subtracting the percent control activity from 100. IC_{50s} were determined by non-linear regression analysis. The data was measured by fluorimetry or HPLC-MS/MS.

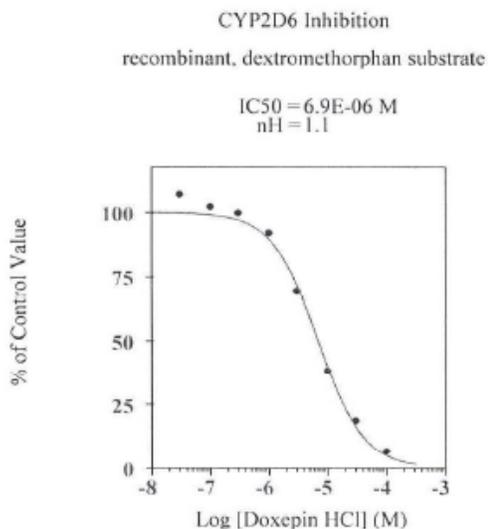
Results:

Below is a summary table of tested results. While the inhibition effect is more evident at the condition using dextromethorphen substrate for CYP2D6 inhibition, the IC₅₀ data and corresponding inhibition curve were shown as well.

Assay (b) (4) Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Values
CYP1A2 Inhibition (recombinant, CEC substrate) 792502-1	Doxepin HCl	1.0E-05	16
CYP2B6 Inhibition (recombinant, EFC substrate) 792502-1	Doxepin HCl	1.0E-05	14
CYP2C8 Inhibition (recombinant, DBF substrate) 792502-1	Doxepin HCl	1.0E-05	23
CYP2C9 Inhibition (recombinant, MFC substrate) 792502-1	Doxepin HCl	1.0E-05	0
CYP2C19 Inhibition (recombinant, CEC substrate) 792502-1	Doxepin HCl	1.0E-05	48
CYP2D6 Inhibition (recombinant, MFC substrate) 792502-1	Doxepin HCl	1.0E-05	49
CYP2E1 Inhibition (recombinant, EC substrate) 792502-1	Doxepin HCl	1.0E-05	-22
CYP1A2 Inhibition (recombinant, phenacetin substrate) 792502-1	Doxepin HCl	1.0E-05	30
CYP2C9 Inhibition (recombinant, diclofenac substrate) 792502-1	Doxepin HCl	1.0E-05	8
CYP2C19 Inhibition (recombinant, omeprazole substrate) 792502-1	Doxepin HCl	1.0E-05	27
CYP2D6 Inhibition (recombinant, dextromethorphan substrate) 792502-1	Doxepin HCl	1.0E-05	64
CYP3A4 Inhibition (recombinant, testosterone substrate) 792502-1	Doxepin HCl	1.0E-05	27
CYP3A4 Inhibition (recombinant, midazolam substrate) 792502-1	Doxepin HCl	1.0E-05	5

IC₅₀ Determination: Summary Results

Assay (b) (4) Compound I.D.	Client Compound I.D.	IC ₅₀ (M)	n _H
CYP2D6 Inhibition (recombinant, dextromethorphan substrate) 792502-1	Doxepin HCl	6.9E-06	1.1



Conclusion:

Doxepin appears to be a weak inhibitor of CYP2D6 with the IC₅₀ at 6.9 μM.

Reviewer's comment: The inhibition of CYP2C8, 2B6 and 2E1 were not evaluated using probe substrates.

Role of P-glycoproteins in the intestinal absorption

A review of the following published paper is summarized for the evaluation of the role of P-gp in the intestinal absorption of drugs. While the paper focuses on the evaluation and characterization of P-gp substrates, this review will focus on the non-substrate drugs, specifically doxepin.

articles



Functional Role of P-Glycoprotein in Limiting Intestinal Absorption of Drugs: Contribution of Passive Permeability to P-Glycoprotein Mediated Efflux Transport

Manthana V. S. Varma, Khandavilli Sateesh, and Ramesh Panchagnula*

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Sector No. 67, SAS Nagar 160 062, Punjab, India

Received August 20, 2004

Method

Different factors and data for a variety of drugs were collected from literature and evaluated for their properties in terms of P-gp mediated intestinal absorption based on the selected factors. The factors were described below.

Permeability: data was collected from two independent preclinical studies. Monolayer efflux studies were performed using multiple resistance transfected MDCK type II cell lines (MDRI-MDCKII).

Efflux ratio (ER, $P_{app,BA}/P_{app,AB}$): used as a basis to classify the bidirectional transport. Drugs with $ER < 1.5$ were considered as non-substrate (NS).

Human intestinal absorption (HIA): Data was collected from literature and standard references.

Solubility, Maximum Dose Strength and Dose number (Do): Do was calculated based on the equation below. Solubility criteria were based on Do with cutoff of $Do \leq 1$ for high solubility and $Do \geq 2$ for low solubility.

$$Do = \frac{Mo}{(Vo)(Cs)}$$

where Mo is the highest dose strength (mg), Cs is the solubility (mg/mL), and Vo is 250 mL, the minimum volume that is available for a formulation to disintegrate and dissolve.

Lipinski's rule-of-5: Physiochemical Properties:

ClogP: ClogP >5 indicates poor absorption or permeability.

Total polar surface area (TPSA): as a descriptor for hydrogen binding and provide relationship to permeability.

Results

A table listed 73 drugs that were classified to be not P-gp substrates (NS) and the respective data for all selected factors. Doxepin was on number 20 with ER, TPSA, ClogP, Do, HIA and BCS class listed as 1.1, 12.5, 4.09, 0.004, 27 and I, respectively.

COPYRIGHT MATERIAL

Conclusion

Doxepin appears to not be a P-gp substrate based on the data summarized in the result.

The N-Demethylation of the Doxepin Isomers Is Mainly Catalyzed by the Polymorphic CYP2C19

A review of the following published paper is summarized for the identification of the CYP450s responsible for the metabolism of doxepin to its major metabolite, N-demethyldoxepin (nordoxepin).

Pharmaceutical Research, Vol. 19, No. 7, July 2002 (© 2002)

The N-Demethylation of the Doxepin Isomers Is Mainly Catalyzed by the Polymorphic CYP2C19

**Sebastian Härtter,^{1,4} Gunnel Tybring,²
Thomas Friedberg,³ Harald Weigmann,¹ and
Christoph Hiemke¹**

Method

Pooled human liver microsomes, chemical inhibitors, and recombinant human-CYPs, and geno- and phenotyped human liver microsomes were utilized for studying the metabolism of doxepin to N-demethyldoxepin.

Results

- More than 50% of the N-demethylation was inhibited (most prominently) by tranylcypromine (CYP2C19).
- N-demethylation was inhibited to a lesser extent by Furafylline (CYP1A2) and sulfaphenazole (CYP2C9).
- There were no effects observed by quinidine (CYP2D6) or troleandomycine (CYP3A4).
- In microsomes, the maximum velocity in the N-demethylation was significantly ($P < 0.05$) lower with low CYP2C19 activity compared to those with high CYP2C19 activity.

Conclusion

The polymorphic CYP2C19 plays a significant role for the N-demethylation of doxepin while CYP2C9 and CYP1A2 play a minor role and CYP3A4 does not contribute substantially.

Role of cytochrome P450 2D6 (CYP2D6) in the stereospecific metabolism of E- and Z-doxepin

A review of the following published paper is summarized for the evaluation of the role of CYP2D6 on the metabolism of E- and Z-doxepin.

Pharmacogenetics 2000, **10**:591–603

Role of cytochrome P450 2D6 (CYP2D6) in the stereospecific metabolism of E- and Z-doxepin

V.S. Haritos^a, H. Ghabrial^b, J.T. Ahokas^a and M.S. Ching^b

^aKey Centre for Applied and Nutritional Toxicology, RMIT-University, Victoria and ^bDepartment of Medicine, University of Melbourne, Austin and Repatriation Medical Centre, Victoria, Australia

Method

Human liver microsomes and recombinant human CYP2D6 were utilized for demonstrating the N-demethylation and hydroxylation of E- and Z-doxepin.

Results

For N-demethylation, the rate of Z-doxepin N-demethylation was found to exceed E-doxepin at the concentration range of 5-1500 μM in human liver microsomes. The Eadie-Hofstee plot suggested that there are several enzymes involved in N-demethylation. Reduced rate of N-demethylation by 30-50% and 40-60% was observed when coincubation with 7, 8-naphthoflavone and ketokonazole, respectively, indicating the involvement of CYP1A2 and CYP3A4 while quinidine demonstrated little effect.

Most importantly, for hydroxylation, it was shown that E-doxepin and E-nordoxepin went through hydroxylation extensively with high affinity in both human liver microsome and recombinant CYP2D6 ($K_m \sim 5-8 \mu\text{M}$) while no evidence for hydroxylation was observed for Z-hydroxylation.

Conclusion

CYP2D6 appeared to be an important oxidative enzyme for doxepin metabolism, specifically for hydroxylation. E-doxepin and E-nordoxepin were predominantly hydroxylated while hydroxylation by CYP2D6 for Z-isomers was not evident.

4.2 OCP REVIEW AND FILING FORM

Office of Clinical Pharmacology			
<i>New Drug Application Filing and Review Form</i>			
General Information About the Submission			
	Information		Information
NDA Number	N 22-036	Brand Name	SILENOR
OCP Division (I, II, III)	DCP-I	Generic Name	Doxepin HCl
Medical Division	HFD-120	Drug Class	Dibenzoxepin Tricyclic agent that acts as a selective histamine H1 antagonist
OCP Reviewer	Veneeta Tandon	Indication(s)	Insomnia
OCPB Team Leader	Ramana Uppoor	Dosage Form	Tablets (1,3 and 6 mg)
		Dosing Regimen	Adults: (b) (4) mg, increased to 6 mg Elderly: (b) (4) mg, increased to (b) (4) and 6 mg
Date of Submission	1/30/08	Route of Administration	Oral
Estimated Due Date of OCP Review	10/12/08	Sponsor	Somaxon Pharmaceuticals
PDUFA Due Date	11/30/08	Priority Classification	Standard
Division Due Date	10/29/08		

Clin. Pharm. and Biopharm. Information

This application for SILENOR™ (Doxepin HCl) is being submitted as a 505(b)(2) submission for the treatment for insomnia. In addition to studies conducted by Somaxon, this NDA relies on safety and efficacy information of NDA 016-798 (Sinequan® Capsules), NDA 017-516 (Sinequan® Oral Concentrate) and NDA 020-126 (Zonalon® 5% Cream), and published literature.

Oral doxepin (Sinequan®) has been marketed in the United States as an antidepressant and anxiolytic at recommended dosages of 75-150 mg/day (Sinequan® NDA Number 016-798, Approved 23 September 1969). Doxepin is also marketed as a Zonalon®, Cream 5%, a topical cream for the treatment of short-term, moderate pruritis with atopic dermatitis or lichen simplex chronicus.

Efficacy of Silenor 1 mg, 3 mg, and 6 mg was evaluated in six adequate and well-controlled studies conducted in 1423 adult and elderly subjects with chronic insomnia (SP-0401, SP-0402, SP-0501, SP-0503 and SP-0509) as well as in healthy adult subjects with experimentally-induced transient insomnia (SP-0502). Assessment of safety also included data from five Phase 1 studies. Across the Silenor clinical development program, 966 individuals were exposed to doxepin.

This NDA consists of

- Five Phase I studies: SP-0405, SP-0504, SP-0505, SP-0506, SP-0507
 1. Dose proportionality with capsules and BE between tablet and capsule (earlier formulation): **DP 1-6 mg, and tablet and capsule were BE**
 2. Food effect with 6 mg: **In the fed state, exposure parameters (AUC_{0-∞} and C_{max}) of doxepin were approximately 41% and 15% higher, respectively, compared to the fasted state, and the median time to reach maximum plasma concentration (T_{max}) was delayed by approximately 3.0 h.: not to be taken with or immediately after a meal**
 3. cimetidine PK DDI (non specific inhibitor): **2 fold increase in doxepin, but little in nordoxepin**
 4. Sertraline PK PD DDI (weak 2D6 inhibitor): **20-30% increase in doxepin C_{max} and AUC**
 5. relative BA with Sinequan capsules: **The relative bioavailability of Silenor was approximately 70% that of Sinequan® based on the AUC_{0-∞}.**
- Two Phase 2 studies: Dose response studies SP-0401 in adults, SP-0402 in elderly
- Four Phase 3 studies: SP-0501, SP-0503 and SP-0509, (SP-0502).

Doxepin HCl is a BCS class I drug, although classification has not been done formally by the Agency. Sponsor does not mention that this product is BCS Class I Drug product.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1	1	Inhibition study
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1	1	Dose Proportionality
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	2	2	cimetidine and sertraline DDI
In-vivo effects of primary drug:	X			
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	Rel BE to Sinequan capsules
Bioequivalence studies -				
traditional design; single / multi dose:	X			capsule versus tablet
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		with 6 mg tablets
Dissolution:				
(IVVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

Chronopharmacokinetics			
Pediatric development plan			
Literature References	27		
Total Number of Studies			
	5 PK + 2 in vitro+ 1 Assay+ Literature		5 PK + 2 in vitro+ 1 Assay+ Literature
<u>Filability and QBR comments</u>			
I.	“X” if yes	<u>Comments</u>	
II. Application filable?		Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
III. Comments sent to firm? IV.	none		
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • Is dose proportionality established in the therapeutic range? • What is the relative bioavailability to the approved doxepin capsules? • Is there any food effect with Silenor? • Is a BE study between the clinical and to-be-marketed necessary? 		
Other comments or information not included above	Induction potential not known Label not completely updated with missing information; e.g. study in hepatic impaired		
Primary reviewer Signature and Date	Veneeta Tandon		
Secondary reviewer Signature and Date	Ramana Uppoor		

Table 5.2 Listing of Clinical Studies

Type of study	Study ID	Location of study report	Objective(s)	Study design; Type of control	Test product(s); Dosage regimen; Route of admin	# subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Food effect	SP-D0504	M5.3.1.1.1	Effects of food on PK	Randomized, open-label, crossover	D6 tablets; Single doses administered fed and fasted; po	16	Healthy subjects	2 days	Complete; Final
Dose linearity	SP-0405	M5.3.1.2.1	PK	Randomized, crossover	D1, D3, D6 capsules, D6 tablets; Single dose of each dose; po	16	Healthy subjects	4 days	Complete; Final
Relative bioavailability	SP-D0507	M5.3.1.2.2	Relative bioavailability of doxepin 6 mg tablets compared to doxepin 50mg capsules	Randomized, open-label, crossover	D6 tablets, doxepin 50 mg capsules; Single dose of each in 2 sequences; po	24	Healthy subjects	2 days	Complete; Final
Drug interaction	SP-D0505	M5.3.3.4.1	PK of doxepin alone and in combination with cimetidine	Open-label, fixed-sequence	D6 tablets, Cimetidine 300 mg; Single doses administered alone and with cimetidine; po	24	Healthy subjects	2 days	Complete; Final
Drug interaction	SP-D0506	M5.3.4.1.1	PK and PD of doxepin alone and in combination with sertraline	Single-blind, double-dummy, fixed sequence	D6 tablets, sertraline 50 mg; Single doses administered alone and in combination with sertraline; po	24	Healthy subjects	2 days	Complete; Final
Efficacy and safety	SP-0401	M5.3.5.1.1	Evaluate sleep maintenance efficacy, safety, and dose response effects of 3 dose levels	Double-blind, randomized, placebo-controlled, multicenter, 4 period crossover	P, D1, D3, D6 capsules; Two consecutive nights dosing of each treatment, at four treatment periods; po	67 (67 drug, 66 placebo)	Chronic primary insomnia	2 nights each at 4 double-blind treatment periods	Complete; Final
Efficacy and safety	SP-0402	M5.3.5.1.2	Evaluate sleep maintenance efficacy, safety, and dose response effects of 3 dose levels in elderly patients	Double-blind, randomized, placebo-controlled, multicenter, 4 period crossover	P, D1, D3, D6 capsules; Two consecutive nights dosing of each treatment, at four treatment periods; po	76 (76 drug, 73 placebo)	Chronic primary insomnia	2 nights each at 4 double-blind treatment periods	Complete; Final

Table 5.2 Listing of Clinical Studies

Type of study	Study ID	Location of study report	Objective(s)	Study design; Type of control	Test product(s); Dosage regimen; Route of admin	# subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy and safety	SP-0501	M5.3.5.1.3	Evaluate efficacy and safety of 2 dose levels administered 35 consecutive nights; Potential rebound and withdrawal effects upon discontinuation	Double-blind, randomized, placebo-controlled, multicenter, parallel group, fixed dose	P, D3, D6 capsules; Single nightly dose of assigned treatment for 35 nights; po	229 (148 drug, 73 placebo)	Chronic primary insomnia	35 nights double-blind dosing	Complete; Final
Efficacy and safety	SP-0502	M5.3.5.1.4	Evaluate sleep onset efficacy and safety of doxepin 6 mg in a model of transient insomnia	Double-blind, randomized, placebo-controlled, multicenter, parallel group, single dose	P, D6 tablets; Single dose of assigned treatment for one night; po	565 (283 drug, 282 placebo)	Healthy subjects	1 night	Complete; Final
Efficacy and safety	SP-0503	M5.3.5.1.5	Evaluate long-term sleep efficacy and safety of 2 dose levels in elderly patients	Double-blind, randomized, placebo-controlled, multicenter, parallel group, fixed dose	P, D1, D3 tablets; Single nightly dose of assigned treatment for 85 nights; po	240 (159 drug, 81 placebo)	Chronic primary insomnia	85 nights double-blind dosing	Complete; Final
Efficacy and safety	SP-0509	M5.3.5.1.6	Evaluate efficacy and safety of doxepin 6 mg administered nightly for 4 weeks in elderly patients	Double-blind, randomized, placebo-controlled, multicenter, parallel group, fixed dose	P, D6 tablets; Single nightly dose of assigned treatment for 28 nights; po	255 (130 drug, 124 placebo)	Chronic primary insomnia	28 nights double-blind dosing	Complete; Final

D1=doxepin 1 mg; D3=doxepin 3 mg; D6=doxepin 6 mg; P=placebo.

Table 2.5.1.1 Overview of Silenor Clinical Study Designs

Study, Location, and Dates	Study Design	Duration of Doxepin Exposure	Subject Population	Primary Efficacy Variable	Secondary Efficacy Variables	Safety Assessments	Treatment/Dose (Number of Subjects in the Safety Analysis Set)
Phase 1 Crossover Daytime Studies in Healthy Volunteers							
SP-0405 1 center in the US 21 May '05– 01 July '05	R, CO, OL, dose proportionality bioequivalence	4 days (1 day on each dose)	Healthy male subjects 18–45 yrs	NA	NA	TEAEs, vital signs, clinical labs, PE, and ECG	Doxepin 1 mg ^a = 15 Doxepin 3 mg ^a = 15 Doxepin 6 mg ^a = 16 Doxepin 6 mg = 16 Total=16
SP-0504 1 center in the US 30 Sep '05– 18 Oct '05	R, CO, OL, food effect	2 days (1 day each condition)	Healthy M/F subjects 18–45 yrs	NA	NA	TEAEs, vital signs, clinical labs, PE, and ECG	Doxepin 6 mg fed = 16 Doxepin 6 mg fasted = 15 Total = 16
SP-0505 1 center in the US 21 Oct '05– 21 Nov '05	FS, CO, OL, cimetidine PK interaction	2 days (1 day each condition)	Healthy M/F subjects 18–45 yrs	NA	NA	TEAEs, vital signs, clinical labs, PE, and ECG	Doxepin 6 mg = 24 Cimetidine 300 mg = 22 Doxepin 6 mg + Cimetidine 300 mg = 22 Total = 24
SP-0506 1 center in the US 21 Jan '06– 08 Feb '06	FS, CO, sertraline PK and PD interaction	2 days (1 day for each condition)	Healthy M/F subjects 18–45 yrs	NA	NA	TEAEs, vital signs, clinical labs, PE, ECG, DSST, SCT, and VAS	Doxepin 6 mg = 24 Sertraline 50 mg = 24 Doxepin 6 mg + Sertraline 50 mg = 24 Total = 24
SP-0507 1 center in the US 02 Dec '05– 22 Dec '05	R, CO, OL, relative bioavailability	1 day (plus 1 day Sinequan [®])	Healthy M/F subjects 18–45 yrs	NA	NA	TEAEs, vital signs, clinical labs, PE, and ECG	Doxepin 6 mg = 23 Sinequan [®] 50 mg capsules = 24 Total = 24

Table 2.5.1.1 Overview of Silenor Clinical Study Designs

Study, Location, and Dates	Study Design	Duration of Doxepin Exposure	Subject Population	Primary Efficacy Variable	Secondary Efficacy Variables	Safety Assessments	Treatment/Dose (Number of Subjects in the Safety Analysis Set)
Phase 2 Chronic Insomnia – Studies Conducted in a Sleep Laboratory							
SP-0401 11 centers in the US Jul '04–Sep '04	DB, R, PC, MC, dose response, 4-period crossover	2 nights each dose 5- or 12-day washout between periods	M/F subjects 18–64 yrs with chronic insomnia	WTDS	WASO, TST, SE, LPS, SE Hr 8, WTAS (by PSG) & sTST, sWASO, LSO	TEAEs, vital signs, clinical labs, PE, ECG, DSST, SCT, VAS, and sleep architecture	Placebo = 66 Doxepin 1 mg ^a = 66 Doxepin 3 mg ^a = 66 Doxepin 6 mg ^a = 67 Total = 67
SP-0402 11 centers in the US Sep '04–Jan '05	DB, R, PC, MC, dose response, 4-period crossover	2 nights each dose 5- or 12-day washout between periods	M/F subjects ≥65 yrs with chronic insomnia	WTDS	WASO, TST, SE, LPS, SE Hr 8, WTAS (by PSG) & sTST, sWASO, LSO	TEAEs, vital signs, clinical labs, PE, ECG, DSST, SCT, VAS, and sleep architecture	Placebo = 73 Doxepin 1 mg ^a = 74 Doxepin 3 mg ^a = 75 Doxepin 6 mg ^a = 74 Total = 76
Phase 3 Chronic Insomnia – Studies Conducted in Sleep Laboratory and Outpatient Settings							
SP-0501 22 centers in the US Jun '05–Dec '05	DB, R, PC, MC, PG, fixed dose	35 nights of DB dosing	M/F subjects 18–64 yrs with chronic insomnia	WASO	WTDS, TST, SE, LPS, SE Hr 8, WTAS, SE last quarter (by PSG) & sTST, sWASO, LSO	TEAEs, vital signs, clinical labs, PE, ECG, DSST, SCT, VAS, rebound insomnia, Tyrer's Symptom Checklist, and sleep architecture	Placebo = 73 Doxepin 3 mg ^a = 75 Doxepin 6 mg ^a = 73 Total = 221
SP-0503 31 centers in the US Sep '05–Sep '06	DB, R, PC, MC, PG, fixed dose	85 nights of DB dosing	M/F subjects ≥65 yrs with chronic insomnia	WASO	WTDS, TST, SE, LPS, SE Hr 8, WTAS, SE last quarter (by PSG) & sTST, sWASO, LSO	TEAEs, vital signs, clinical labs, PE, ECG, DSST, SCT, VAS, and sleep architecture	Placebo = 81 Doxepin 1 mg = 77 Doxepin 3 mg = 82 Total = 240

Table 2.5.1.1 Overview of Silenor Clinical Study Designs

Study, Location, and Dates	Study Design	Duration of Doxepin Exposure	Subject Population	Primary Efficacy Variable	Secondary Efficacy Variables	Safety Assessments	Treatment/Dose (Number of Subjects in the Safety Analysis Set)
Phase 3 Chronic Insomnia – Study Conducted in an Outpatient Setting							
SP-0509 32 centers in the US Jan '06–Sep '06	DB, R, PC, MC, PG, fixed dose	28 nights of DB dosing	M/F subjects ≥65 yrs with chronic insomnia	sTST	LSO and sWASO	TEAEs, vital signs, clinical labs, PE, and ECG	Placebo = 124 Doxepin 6 mg = 130 Total = 254
Phase 3 Transient Insomnia – Study Conducted in a Sleep Laboratory							
SP-0502 6 centers in the US Feb '06–Jun '06	DB, R, PC, MC, PG, single-dose	1 night of DB dosing	Healthy M/F subjects 25–55 yrs with induced transient insomnia	LPS	WASO, WTDS, TST, SE, SE Hr 8, WTAS, SE last quarter (by PSG) & sTST, sWASO, LSO	TEAEs, acute vital signs, clinical labs, PE, ECG, DSST, SCT, VAS, and sleep architecture	Placebo = 282 Doxepin 6 mg = 283 Total = 565

Table 2.7.1.3 Quantitative Composition per Tablet of Uncolored CTM, Registration and Proposed Commercial Batches

Ingredient	1 mg Tablet			3 mg Tablet		6 mg Tablet	
	CTM	Registration (Yellow)	Commercial (Yellow)	CTM	Registration & Commercial (Blue)	CTM	Registration & Commercial (Green)
Doxepin HCl, USP	(b) (4)	(b) (4)	(b) (4)	3.390 ²	3.390	6.780 ⁴	6.780
Magnesium Stearate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
D&C Yellow No. 10	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
FD&C Blue No. 1	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight	(b) (4)	(b) (4)	(b) (4)	(b) (4)	150	150	150

¹ Equivalent to 1.0 mg of doxepin as the free base

² Equivalent to 1.03 mg of doxepin as the free base

³ Equivalent to 3.0 mg of doxepin as the free base

⁴ Equivalent to 6.0 mg of doxepin as the free base

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/s/

Ju-Ping Lai
11/6/2008 10:47:05 AM
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Veneeta Tandon
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BIOPHARMACEUTICS

Mehul Mehta
1/6/2009 03:38:58 PM
BIOPHARMACEUTICS

Biopharmaceutics Review

NDA:	22-036
Submission Date:	January 30, 2008
Type of Submission:	3S
Product name	Silenor™ (doxepin HCl)
Dosage Form:	Tablet
Dosage Strengths:	1 mg, 3 mg, and 6 mg
Sponsor:	Somaxon Pharmaceuticals, Inc.

Background

The CMC reviewer asked that a review be conducted to determine whether doxepin HCl qualifies as a highly soluble and highly permeable drug according to the Biopharmaceutics Classification System.

Silenor (doxepin HCl) is indicated for the treatment of insomnia. It is an immediate release tablet in three strengths (1 mg, 3 mg, and 6 mg). The tablet formulation was developed using standard (b) (4). The main differences between the capsule used in early clinical development and the tablet formulation is the presence of (b) (4) in the tablet that possess (b) (4).

In this submission, the sponsor is planning to add a colored, (b) (4) film-coat as a mean to visually distinguish between different strengths. However, in order to make this addition, the sponsor has to perform other changes to the manufacturing process, including the following:

(b) (4)

The sponsor submitted the following information to assess the solubility and permeability of Doxepin and concluded that Doxepin is highly soluble and

highly permeable drug substance according to the Biopharmaceutics Classification System.

Assessing Solubility

The sponsor determined the intrinsic solubility of doxepin HCl potentiometrically using a ^{(b) (4)} titration methodology. All experiments were titrated from low to high pH, and precipitate was observed. The sponsor reported that the observed solubility ranged from 649 mg/250 mL at pH=7.5 to 19 mg/250 mL at pH=11.9, and concluded that according to Henderson-Hasselbach theory, when the potentiometrically-generated solubility data are plotted in the range of pH 1 to 7.5, doxepin HCl clearly demonstrates solubility values consistent with a Class 1 molecule as defined in the Biopharmaceutic Classification System (BCS).

Reviewer's Note:

The sponsor did not use sufficient number of pH conditions to define the pH solubility profile. Depending on the pKa of doxepin, the solubility should be determined at pH = pKa, pH = pKa +1, pH = pKa -1, and at pH 1 and 7.5. The sponsor did not provide the solubility data/profile generated and did not mention whether concentrations of the drug substance in selected buffers (or pH conditions) were determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.

Assessing Permeability

The sponsor determined the in-vitro permeability of doxepin HCl, USP using Caco-2 human colonic-derived cell line.

When the highest dose of doxepin HCl (i.e. 6 mg) is dissolved in 250 mL, the resulting concentration is 76 µM. Due to analytical method sensitivity, the doxepin HCl concentrations tested in these permeability experiments were 100 µM, 10 µM and 1 µM. Table 1 presents the permeability data for these three concentrations of drug.

Table 1. Doxepin HCl, USP A-to-B Permeability as a Function of Concentration

Nominal Doxepin HCl Dosing Concentration (µM)	1	10	100
Permeability (10^{-9} cm/sec)	17.7 ± 1.99	23.2 ± 1.05	37.6 ± 1.19
Recovery (%)	57.4 ± 4.39	64.5 ± 2.59	77.7 ± 3.13

The mean recoveries of doxepin HCl at all three tested concentrations were relatively low, ranging from 57.4% to 77.7%. The sponsor stated that these results indicate that some doxepin HCl adhered to the device and/or accumulated in the cells. Subsequent mass balance experiments demonstrated

the intracellular accumulation of doxepin HCl in the cells of Caco-2 monolayers as seen in Table 2 below.

Table 2. Mass Balance Results

Dosing (μM)	Direction	Mean Doxepin HCl Concentration (μM)				Mass Balance (%)
		Measured Dosing	Receiver at 45 min	Donor at 45 min	Lysate	
1	A-to-B	1.08	0.0404	0.512	0.394	95.1%
	B-to-A		0.141	0.829	0.266	89.4%
10	A-to-B	10.9	0.508	5.42	2.74	88.9%
	B-to-A		1.82	9.00	2.19	94.8%
100	A-to-B	105	7.81	59.4	18.0	96.2%
	B-to-A		26.3	90.5	11.8	98.5%

A-to-B permeability values for doxepin HCl increased as the dosing concentrations increased. The recovery of doxepin HCl followed the same pattern. The sponsor stated that the increased permeability at higher concentrations of doxepin HCl is solely caused by the intracellular accumulation phenomenon which is more significant at lower drug concentrations.

The sponsor stated that the lack of directional dependence [i.e. basolateral-to-apical (B-to-A) versus apical-to-basolateral (A-to-B)] of drug substance permeability in cell monolayers expressing efflux transporters is also an evidence of a passive transport mechanism. Table 3 presents the doxepin HCl bidirectional permeability data.

Table 3. Doxepin HCl, USP Bidirectional Permeability

Nominal Doxepin HCl Dosing Concentration (μM)	1	10	100
A-to-B permeability (10^{-6} cm/sec)	17.7 ± 1.99	23.2 ± 1.05	37.6 ± 1.19
B-to-A permeability (10^{-6} cm/sec)	22.6 ± 2.53	27.4 ± 2.56	36.6 ± 6.40
B-to-A vs. A-to-B permeability ratio	1.28	1.18	0.974

The experiments included low and highly permeable drugs, atenolol and pindolol respectively, as reference compounds. These reference compounds have fractional absorption in humans of about 50% and 90% respectively.

Table 4 presents the measured A-to-B permeabilities of doxepin HCl, and the internal control compounds pindolol and atenolol.

Table 4. A-to-B Permeability of Doxepin HCl, Pindolol and Atenolol

Nominal Doxepin HCl Dosing Concentration (μM)		1	10	100
Doxepin HCl	Permeability (10^{-6} cm/sec)	17.7 ± 1.99	23.2 ± 1.05	37.6 ± 1.19
	Recovery (%)	57.4 ± 4.39	64.5 ± 2.59	77.7 ± 3.13
Pindolol	Permeability (10^{-6} cm/sec)	11.4 ± 1.05	9.10 ± 0.536	12.5 ± 1.02
	Recovery (%)	93.8 ± 2.26	91.0 ± 2.77	96.0 ± 2.86
Atenolol	Permeability (10^{-6} cm/sec)	0.143 ± 0.0654	0.198 ± 0.0462	0.266 ± 0.120
	Recovery (%)	87.7 ± 3.23	89.4 ± 3.52	90.6 ± 2.96

The permeability rank order of doxepin HCl and the reference compounds was doxepin HCl > pindolol > atenolol at all three concentrations.

Reviewer's Note:

Since the permeability of the doxepin HCl was much higher than pindolol, which has a reported absorption in humans of 90%, it can be inferred that doxepin HCl is considered a highly permeable drug substance.

Assessing Dissolution

The sponsor performed disintegration and dissolution testing for doxepin tablets to assess the effect of changing tablet compression force on dissolution. The change to (b) (4) was proposed to (b) (4). Table 5 below shows dissolution as a function of tablet hardness.

Table 5. Silenor Disintegration and Dissolution as a Function of Tablet Hardness

(b) (4)

Reviewer's Note:

Although this review did not assess whether dissolution testing suffices as evidence of equivalency between product before and after the change, the dissolution data in Table 5 above indicates that tablet disintegration time

(b) (4)

Disintegration in this case seems to be a more sensitive test than dissolution to assess the effect of a change on drug product quality.

Comments to Chemistry Reviewer

A preliminary review was performed of the following information provided by the CMC Reviewer, Dr. Sherita McLamore:

- Section 3.2.S.1.3. General Properties (doxepin HCl, USP, Plantex LtdL)
- Section 3.2.R.2.P. Comparability Protocol
- Study Report No: 7SOMAP2R@GLPS43

Doxepin could not be classified as Class I (Highly Soluble and Highly Permeable) drug product for the following reasons:

(b) (4)

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.
Biopharmaceutics Expert
Office of New Drug Quality Assessment

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Houda Mahayni
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Patrick Marroum
11/28/2008 10:22:19 AM
BIOPHARMACEUTICS

Executive CAC

Date of Meeting: November 4, 2008

Committee: David Jacobson-Kram, Ph.D., D.A.B.T., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Alternate Member
Lois M. Freed, Ph.D., DNP, Supervisory Pharmacologist
Melissa K. Banks, Ph.D., DNP, Presenting Reviewer

Coordinator: Sam Habet, R.Ph., Ph.D., OND IO, Senior Clinical
Pharmacologist/ Science Policy Analyst (Detail)

Author of Draft: Melissa K. Banks, Ph.D.

NDA #: 22-036

Date of Submission: January 30, 2008

Drug Name: Silenor™, doxepin hydrochloride

Sponsor: Somaxon Pharmaceuticals

The following information reflects a brief summary of the Committee discussion and conclusions:

Doxepin is a tricyclic compound exerting histamine (H₁) receptor antagonism, which is currently being developed as a sedative-hypnotic; it is FDA approved as an antidepressant and anxiolytic (as Sinequan®) and for the treatment of atopic dermatitis & lichen simplex chronicus (as Zonalon®). Based on results of an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberrations assay (HPBL) and an *in vivo* rat micronucleus assay, doxepin is not genotoxic. To evaluate the potential for carcinogenicity, the sponsor performed a 26-week transgenic mouse assay in Tg.rasH2 mice; Executive CAC concurrence on the doses used in the study was not requested prior to initiation of the study.

Mouse Carcinogenicity Study

Doxepin was administered orally (by gavage) at doses of 0 (vehicle: water for injection), 25, 50, 75 and 100 mg/kg in male and female transgenic Tg.rasH2 mice for 26 weeks. Survival rate was not significantly affected, although mortality rate was slightly increased in high dose males. A slight but statistically significant and dose-related decrease in mean body weights was observed. At the high dose, mean body weight was reduced by 9-13% compared to controls. The high dose appeared to be an MTD in males and females, based on body weight and clinical signs; data from previous studies indicate that higher doses were not tolerated. Histopathological evaluation of a full battery of tissues was performed on all control and doxepin-treated groups. Neoplasms were detected in the nasal cavity (adenocarcinomas), lung (adenomas and carcinomas) and spleen (hemangiosarcomas), but not in a dose-related manner. The sponsor considered the occurrence of nasal cavity and splenic tumors to be “noteworthy”, but concluded that

doxepin was not tumorigenic. Urethane-treated positive controls were used to verify the sensitivity of the assay; the expected increases in pulmonary and splenic neoplasms were observed.

Executive CAC Conclusions

The Committee concurred that the study was adequate and that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D., D.A.B.T.
Chair, Executive CAC

cc:\

- /Division File, DNP
- /LFreed, DNP
- /MBanks/Reviewer, DNP
- /CMichaloski/CSO/PM, DNP
- /DJacobson-Kram/OND, IO
- /SHabet/OND IO

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Sayed Al-Habet
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David Jacobson-Kram
11/6/2008 03:48:40 PM
PHARMACOLOGIST