

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022036Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 8, 2010

To: Russell Katz, MD, Director
Division of Neurology Products

Thru: Melina Griffis, R.Ph, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Lubna Najam, M.S., PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Silenor (Doxepin Tablets)
3 mg, and 6 mg

Application Type/Number: NDA 022036

Applicant: Somaxon Pharmaceuticals, Inc.

OSE RCM #: 2008-1836

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INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Silenor (OSE RCM #2008-96) on October 23, 2008 in which we made recommendations regarding the proposed container labels and carton labeling. The Applicant submitted their revisions dated December 15, 2008 addressing DMEPA's requested changes which were found to be acceptable (OSE RCM #2008-1836) on January 13, 2009. Subsequently, the applicant has submitted revised carton labeling, container and blister pack labels in addition to new physician sample pack.

1 METHODS AND MATERIAL REVIEWED

In a submission dated February 25, 2010, the applicant has submitted revised container labels and carton labeling to incorporate the required medication guide statement. In addition this submission contained new physician sample pack labels, which were not previously reviewed by DMEPA. Our review of the container labels and trade blister pack labels and carton labeling was limited to the evaluation of the medication guide statement since these labels and labeling were previously found to be acceptable (OSE RCM #2008-1836) on January 13, 2009. However the physician sample blister pack label and labeling was fully evaluated since they were not previously reviewed by DMEPA. Using Failure Mode and Effects Analysis (FMEA),¹ we evaluated the blister physician sample pack label and labeling. See Appendices A through C for pictures of the labels and labeling.

- Commercial Bottle Labels (3 mg, 6 mg)
- Trade Pack Blister Card Label and Carton Labeling
- Physician Sample Blister Card Label and Carton Labeling (4 and 7 count samples)

2 CONCLUSIONS AND RECOMMENDATIONS

We provide recommendations in Section 2.1 and request they be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

2.1 COMMENTS TO THE APPLICANT

A. General Comment (all labels)

In accordance with 21 CFR 201.10 (g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Bottle Container Label (3 mg and 6 mg)- 30, 100 and 500 tablet containers

1. The medication guide statement is currently displayed (b) (4) and is difficult to identify and read. In accordance with 21 CFR 208.24 (2)(d) the medication guide statement should appear in a prominent and conspicuous manner on the label. Relocate the medication guide statement to the principal display panel on the label. This statement should not intervene with other pertinent information, e.g. strength, established name and proprietary name and should also not decrease the prominence of this information.
2. Please ensure that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription.

C. Physician Sample Blister Carton Labeling (3 mg and 6 mg) 4 and 7 count samples

In several instances the proprietary and established names are displayed without the strength presentation or vice versa. Revise these labels to ensure that the product strength appears in conjunction with the proprietary and established names.

D. Physician Sample Blister Pack Label (3 mg and 6 mg) 4 and 7 count samples

Increase the font size of the statement “Each tablet contains the equivalent of 3 mg doxepin” present on both the 3 mg and 6 mg blister card label to increase its prominence.

13 pp of Draft Labeling have been withheld in full as b4 (CCI/TS)
immediately following this page.

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

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/s/

LUBNA NAJAM
03/09/2010

MELINA N GRIFFIS
03/09/2010

DENISE P TOYER
03/09/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 9, 2009

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Mary Willy, PhD, Deputy Division Director
Division of Risk Management (DRISK)
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

From: Melissa Hulett, MSBA, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): SILENOR (doxepin hydrochloride) tablets

Application Type/Number: NDA 22-036

Applicant/sponsor: Somaxon Pharmaceuticals, Inc.

OSE RCM #: 2008-1663

1 INTRODUCTION

Somaxon Pharmaceuticals, Inc. originally submitted a 505 (b) (2) New Drug Application (NDA), NDA 22-036, for SILENOR (doxepin hydrochloride) tablets, on January 31, 2008. The NDA was reviewed by the Division of Neurology Products (DNP) and it was determined that the application could not be approved in the present form. The Agency issued a Complete Response letter outlining the deficiencies in the application on February 25, 2009. The Applicant submitted a Complete Response to the Agency's Complete Response letter for SILENOR (doxepin hydrochloride) tablets on June 4, 2009. SILENOR (doxepin hydrochloride) tablets are indicated for the treatment of insomnia as demonstrated by improvement in sleep maintenance and the (b) (4). The active ingredient in SILENOR is doxepin hydrochloride, the same active ingredient in Sinequan and multiple generic antidepressant drug products. Sinequan and the multiple generic products currently carry the single issue antidepressant Medication Guide (MG) which addresses suicidality. Since SILENOR (doxepin hydrochloride) tablets acts as a sedative-hypnotic when dosed according to the PI, DNP proposes a comprehensive MG for the product which includes language related to suicidality, as well as complex behaviors and other product specific information.

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed MG for SILENOR (doxepin hydrochloride) tablets.

Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft SILENOR (doxepin hydrochloride) Prescribing Information (PI) submitted June 4, 2009 and revised by the Review Division throughout the current review cycle.
- Draft SILENOR (doxepin hydrochloride) Medication Guide (MG) submitted on June 4, 2009 and revised by the review division throughout the review cycle.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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

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/s/

MELISSA I HULETT
11/09/2009

MARY E WILLY
11/09/2009
I concur



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 13, 2009

To: Russell Katz, MD, Director
Division of Neurology Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Jinhee J. Lee, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Silenor (Doxepin Tablets)
1 mg, 3 mg, and 6 mg

Application Type/Number: NDA 22-036

Applicant: Somaxon Pharmaceuticals, Inc.

OSE RCM #: 2008-1836

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Silenor (OSE RCM #2008-96) on October 23, 2008 in which we made various recommendations regarding the proposed container labels and carton labeling. On December 5, 2008, DMEPA thereafter had an informal teleconference with the Applicant in which our label/labeling recommendations were conveyed. Subsequently, the Applicant submitted their revisions dated December 15, 2008 addressing DMEPA's requested changes.

2 MATERIAL REVIEWED

DMEPA reviewed our initial labeling review for Silenor on October 23, 2008 in OSE RCM #2008-963 and we also reviewed the revised labels submitted by the Applicant dated December 15, 2008. See Appendices A through C for pictures of the labels and labeling.

- Commercial Container Labels (1 mg, 3 mg, 6 mg)
- Commercial Blister Carton Labeling
- Sample Blister Carton Labeling (4 and 7 count samples)

3 DISCUSSION

The Applicant has changed the container labels and carton labeling according to our recommendations and we have no further comments.

4 CONCLUSIONS AND RECOMMENDATIONS

The Applicant has satisfactorily revised the labels and labeling per our August 2008 request.

If you have further questions or need clarifications, please contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

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/s/

Jinhee Lee
1/13/2009 02:02:55 PM
DRUG SAFETY OFFICE REVIEWER

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MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: November 12, 2008

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: Evaluation of Abuse Potential of Doxepin (Silenor)
Labeling Recommendations
NDA 22-036
Indication: Treatment of Insomnia (1, 3 and 6 mg/day)
Sponsor: Somaxon Pharmaceuticals, Inc.

Materials Reviewed:

CSS has reviewed abuse potential-related sections of the NDA for doxepin, references available in the medical and scientific literature, and data in the Drug Abuse Warning Network (DAWN) Live! epidemiological database for this consult.

Background:

This consult responds to a request by the Division of Neurology Products for an abuse potential assessment of doxepin (NDA 22-036), to help determine appropriate labeling of the drug and to assess whether the drug should be recommended for scheduling.

Doxepin is proposed for the treatment of insomnia at an oral daily dose of 1, 3 or 6 mg, under the tradename Silenor. The mechanism of action of doxepin is primarily as an antagonist at H1 histamine receptors, but it also has activity as an inhibitor of the serotonin and norepinephrine transporters, as an antagonist at serotonin 5-HT2A and 5-HT2C, and as an antagonist at acetylcholine muscarinic receptors. Doxepin is currently marketed in the U.S. as a nonscheduled drug for the treatment of depression (Sinequan, 75 mg tablets) and for the treatment of pruritis secondary to eczematous dermatoses (Zonalon, 5% cream). The Sponsor proposes that doxepin not be scheduled under the Controlled Substances Act.

In November 2005, the Sponsor submitted a 14-page “position paper” to CSS regarding the abuse potential of doxepin, accompanied by the drug label for Sinequan. In this document, the Sponsor provided arguments supporting their conclusion that doxepin is not a drug of abuse. Subsequently, in a pre-NDA meeting in May 2006, the Sponsor was informed that, “The information submitted by the Sponsor [in the position paper] regarding abuse liability is acceptable. CSS concurs with the Sponsor’s conclusions that low-dose doxepin has minimal abuse potential and that Silenor tablets should not be scheduled. Further testing regarding abuse liability potential (sic) for this NDA is unnecessary.”

Conclusion:

CSS has evaluated the abuse-related data submitted in the NDA and reiterates our previous conclusion that doxepin does not have abuse potential and should not be recommended for scheduling.

Drug Label Recommendations:

1) The label text proposed by the Sponsor for Section 9.0 should be changed. CSS proposes the following text:

9.0 Drug Abuse and Dependence

9.1 Controlled Substance Class

Doxepin is not a controlled substance.

(b) (4)

9.2 Abuse

Doxepin is not associated with abuse potential in animals or in humans. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of doxepin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence

In a brief assessment of adverse events observed during discontinuation of doxepin following chronic administration, no symptoms indicative of a withdrawal syndrome were observed. Thus, doxepin does not appear to produce physical dependence.

APPENDIX

Summary of Preclinical and Clinical Information Submitted Related to the Abuse Potential Assessment of Doxepin

This section provides summaries of the abuse potential-related information on doxepin submitted in NDA 22-036, followed by a discussion of the submitted material.

I. Summary of Information Related to Abuse Potential from Preclinical Studies

The Sponsor did not conduct any abuse-related preclinical studies with doxepin. Thus, no primary data were submitted from receptor binding studies or animal behavioral studies (including drug discrimination or self-administration) that are useful in the assessment of abuse potential. Additionally, no primary data were submitted regarding the preclinical evaluation of physical dependence with doxepin.

Instead, the Sponsor conducted a search of papers published in the scientific and medical literature reporting on preclinical studies related to doxepin. This search produced a list of studies related to receptor binding and functionality, second messenger systems, pain response and safety pharmacology. Of these, only the receptor binding studies contain relevant information to the assessment of abuse potential. These published studies are summarized below (references cited below are provided as complete papers in the NDA).

Doxepin has very high affinity (0.3 nM in human brain tissue; Kanba and Richelson, 1984) for the H1 histamine receptor, where it acts as an antagonist. It also has relatively high affinity for the 5-HT2A receptor (26 nM in rodent cell line; Palvimaki et al., 1996) the 5-HT2C receptor (72 nM in porcine brain tissue; Jenck et al., 1994) and the acetylcholine muscarinic receptor (23 nM; Cusack et al., 1994) and acts as an antagonist at all three receptors. It has only moderate-to-low affinity for the dopamine D2 receptor (360 to 2400 nM in human brain tissue; Cusack et al., 1994 and Richelson and Nelson, 1984), where it may act as a weak agonist or antagonist. Doxepin also acts an inhibitor of two monoamine transporters, the serotonin transporter (68 nM in human cell line; Tatsumi et al., 1997) and norepinephrine transporter (30 nM in human cell line; Tatsumi et al., 1997). However, doxepin shows no affinity for the dopamine transporter (>5700 nM; Richelson and Pfenning, 1984), GABA transporter (>31,000 nM; Nakashita et al., 1997), benzodiazepine receptors (>1000 nM; Heal et al., 1992) or opioid receptors (>10,000 nM; Wong et al., 1983).

CSS conducted an independent literature search on preclinical studies with doxepin related to abuse potential. The binding studies reported by the Sponsor in the NDA correctly represent the studies reported in the medical and scientific literature. No papers are listed in PubMed that report on self-administration studies with doxepin. There is one paper reporting on a drug discrimination study conducted with doxepin in pigeons (Zhang and Barrett, 1991). In this study, doxepin produced generalization to the cue produced by the tricyclic antidepressant imipramine, demonstrating that doxepin has similarity to another drug with serotonin-norepinephrine reuptake inhibitor (SNRI) properties.

However, no drug discrimination studies evaluating the similarity between doxepin and known drugs of abuse have been published.

In conclusion, there is very limited information provided in the NDA and identified in the scientific and medical literature related to the assessment of doxepin's abuse potential. However, based on the receptor binding studies and a single drug discrimination study, there is no suggestion that doxepin has similarity to known drugs of abuse.

II. Summary of Information Related to Abuse Potential from Clinical Studies

The Sponsor did not conduct any abuse-related clinical studies with doxepin. Thus, the only available information submitted in relation to the human abuse potential of doxepin is the adverse events (AE) profile observed during clinical efficacy studies. Additionally, the Sponsor conducted a brief evaluation of withdrawal following discontinuation of doxepin after 35 days of administration.

Clinical Efficacy Studies with Doxepin in Patients with Insomnia

During Phase 3 clinical efficacy studies, a total of 437 patients with insomnia received doxepin at doses of 1, 3 or 6 mg/day. As expected from a drug being developed for the treatment of insomnia, the most frequent CNS-related AE was somnolence (5.5%). All other psychiatric and neurological AEs had an incidence of less than 2%. Thus, no AEs related to abuse potential, including euphoria, were observed during administration of doxepin at doses of 6 mg/day or less.

Assessment of Withdrawal Following Doxepin Discontinuation

The Sponsor conducted a study in which withdrawal signs and symptoms were assessed following a 35-day administration of doxepin at 3 and 6 mg/day to patients with insomnia. On Days 36 and 37 of the study, patients received placebo instead of doxepin and were monitored for rebound insomnia (using ECG recordings and Wake After Sleep Onset (WASO) assessments) and for withdrawal (using Tyler's Symptom Checklist, which was formerly known as the Benzodiazepine Withdrawal Symptom Questionnaire). Additionally, AEs reported during this two-day period were also monitored.

During the two-day drug discontinuation period, a total of 4 subjects of 73 (5%) who received the 6 mg/day dose of doxepin experienced intermittent gastrointestinal distress, including nausea and vomiting. The investigator determined that only 2 of these patients (2.5%) had the AE that was directly related to doxepin. In the group of patients who received the 3 mg/day dose of doxepin, 2 of 75 (3%) experienced an increase in glucose levels and 1 of 75 (1%) experienced a headache upon drug discontinuation. In the placebo group, 1 patient of 73 (1%) experienced gastrointestinal distress, and 2 of 73 (3%) experienced headache.

Data from Tyler's Symptom Checklist show that none of the patients in any of the treatment groups experienced benzodiazepine-like withdrawal AEs upon doxepin

discontinuation. However, rebound insomnia (defined as a change from baseline of greater than 35 minutes) was observed in patients in all three treatment groups on the first night after drug discontinuation, with an incidence of 10% in 6 mg doxepin group, 15% in 3 mg doxepin group and 9% in placebo group.

Overall, the reports of AEs experienced during the discontinuation phase following chronic doxepin administration do not suggest that doxepin produces a withdrawal syndrome. Thus, doxepin does not appear to produce physical dependence.

III. Summary of Epidemiological Information Related to Abuse Potential

The Sponsor did not submit any information from epidemiological databases. However, CSS conducted an independent review of data in the Drug Abuse Warning Network (DAWN), a public health surveillance system sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) that monitors drug-related visits to hospital emergency departments (EDs) to track the impact of drug use, misuse and abuse in the U.S. When a DAWN analysis was conducted for doxepin, the number of ED episodes for case types related to abuse potential was below the cut-off for validity because of variability in the reporting system. Thus, the DAWN data do not support the contention that doxepin is associated with adverse events related to abuse potential that necessitate emergency medical care.

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/s/

Katherine Bonson
11/12/2008 04:32:55 PM
PHARMACOLOGIST

Michael Klein
11/20/2008 01:03:36 PM
PHARMACOLOGIST

**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

P/T REVIEWER: Melissa Banks, Ph.D.
DATE: October 28, 2008
NDA: 22-036
DRUG CODE#: doxepin HCl
CAS#: 1229-29-4
DIVISION(s): Div. of Neurology Products; HFD-120
DRUG NAME(s): Silenor™
SPONSOR: Somaxon Pharmaceuticals
3721 Valley Centre Drive, Suite 500
San Diego, CA 92130
T: 858-480-0400, F: 858-509-1761
www.somaxon.com

LABORATORY:



CARCINOGENICITY STUDY

REPORT DATE: 1/24/08

THERAPEUTIC CATEGORY: Insomnia- Hypnotic
FDA approved as an antidepressant & anxiolytic as Sinequan® and treatment of atopic dermatitis & lichen simplex chronicus as Zonalon®

PHARMACOLOGICAL /

CHEMICAL CLASSIFICATION: dibenzoxepin tricyclic, histamine H₁ antagonist

MUTAGENIC/GENOTOXIC: Not genotoxic

[Based on results of *in vitro* bacterial reverse mutation assay, *in vitro* chromosomal aberrations assay (HPBL) and *in vivo* rat micronucleus assay]

Note:

RAT CARCINOGENICITY STUDY: 2-yr Bioassay Pending

The protocol for the 2-yr. rat carcinogenicity bioassay was submitted for ExecCAC concurrence (SN057, dated 6/19/07); the ExecCAC meeting was held 7/31/07 and the meeting minutes (dated 8/1/07) were faxed to the sponsor.

MOUSE CARCINOGENICITY STUDY:

Sponsor initiated study without ExecCAC concurrence on doses.

MOUSE STUDY DURATION: 26 weeks (183-183 days) control- and doxepin-treated; 114/116 days for urethane-treated positive control

STUDY STARTING DATE: 4/16/07

STUDY ENDING DATE: 1/4/08

MOUSE STRAIN: Tg.rasH2 mice

ROUTE: Oral gavage
(urethane pos. control, 1000 mg/kg, 3x IP)

DOSING COMMENTS: QD for 182 days

NUMBER OF MICE: 25/sex/gp main study
(TK: 5/sex/gp control, 35/sex/gp doxepin)

MOUSE DOSE LEVELS (mg/kg/day): 0 (vehicle), 25, 50, 75 & 100 mg/kg/day

BASIS FOR DOSES SELECTED: MTD, based on 5- and 28-day study

- In 28-day study, MTD = 50 mg/kg, based on moderately severe clinical signs (e.g., comatose, dyspnea) that resolved by D12-D13
- In 5-day study, “prolonged” clinical signs (@ 100) and mortality (@150)

PRIOR FDA DOSE CONCURRENCE: None (see explanation below)

The 26-week oral carcinogenicity transgenic (Tg.rasH2) mouse protocol was submitted as special protocol for concurrence by the ECAC (SN055, dated 4/26/07), but was denied because the study was already ongoing.

MOUSE CARCINOGENICITY:

The sponsor (and FDA statistical reviewer) concluded that doxepin hydrochloride was not tumorigenic in Tg.rasH2 mice administered the drug daily for 26 weeks, based on: 1) a lack of statistical difference between tumor frequencies in doxepin treatment groups and vehicle controls and 2) the lack of dose- or exposure-dependence for the doxepin group tumors (nasal cavity, lung and spleen). The sponsor considered the development of splenic hemangiosarcomas and nasal adenocarcinomas in doxepin groups “noteworthy” because these tumors were not observed in the concurrent vehicle controls.

Mortality was not statistically increased in the doxepin-treated groups, although there appeared to be a slight increase in HDM (3/25), compared to vehicle controls (0/25); mortality in the HDM TK group supported an effect. Increased mortality was observed in the urethane-treated positive controls. “Comatose” was only reported through day 8, but other clinical signs persisted (e.g., labored breathing/dyspnea, lethargy, decreased motor activity, rapid/shallow breathing). Group mean body weights were statistically significantly and dose-dependently reduced in doxepin treated groups; reductions on day 183 ranged from 6.2-13.2% in males and 5.1-9.5% in females, compared to controls. Complete histopathology was performed on all control and doxepin-treated groups; select tissues were assessed from the positive control animals.

MOUSE TUMOR FINDINGS: None statistically significant by FDA review

In the doxepin-treated animals, possibly drug-related neoplastic alterations were observed in the nasal cavity, the lung and the spleen.

In addition to the acute inflammatory lesion observed in vehicle controls and the chronic-active inflammation noted in the nasal cavity of doxepin-treated animals, hyperplastic and neoplastic lesions (adenocarcinomas) were noted in the nasal cavities of doxepin-treated animals of both sexes. See the sponsor’s summary table 25, below, for details.

Table 25 - Incidence of Microscopic Nasal Cavity Lesions in rasH2 Mice

	Vehicle	Doxepin 25 mg/kg/day	Doxepin 50 mg/kg/day	Doxepin 75 mg/kg/day	Doxepin 100 mg/kg/day
Males					
Number Examined	25	25	25	25	25
Chronic-Active Inflammation					
Minimal	0	16	14	18	18
Mild	0	0	2	2	6
Moderate	0	0	6	4	0
Submucosal Gland Hyperplasia					
Minimal	0	15	7	8	16
Mild	0	8	16	14	7
Moderate	0	0	1	2	2
Squamous Metaplasia with Hyperplasia					
Minimal	0	21	19	23	23
Mild	0	2	2	1	2
Moderate	0	0	3	0	0
Adenocarcinoma					
	0	2	0	0	0
Females					
Number Examined	25	25	25	25	24
Chronic-Active Inflammation					
Minimal	1	12	14	12	5
Mild	0	1	2	9	9
Moderate	0	0	4	3	8
Submucosal Gland Hyperplasia					
Minimal	0	15	8	6	9
Mild	0	5	10	13	11
Moderate	0	0	4	5	2
Squamous Metaplasia with Hyperplasia					
Minimal	0	13	15	20	19
Mild	0	4	5	3	2
Moderate	0	0	2	1	1
Adenocarcinoma					
	0	1	2	1	0

Note: Multiple adenomas and/or carcinomas were present in the same animal in urethane treated mice
 * p<0.05 (Fisher’s Exact Test) compared to vehicle controls (Group 1).

Doxepin-treated animals were observed to have adenomas and carcinomas of the lung. Pulmonary tumors are spontaneous tumors known to occur in this strain of mouse. See the sponsor’s summary table 23, next page.

Table 23 - Incidence of Pulmonary Tumors in rasH2 Mice

	Vehicle	Urethane 1000 mg/kg/day	Doxepin 25 mg/kg/day	Doxepin 50 mg/kg/day	Doxepin 75 mg/kg/day	Doxepin 100 mg/kg/day
Males						
Number Examined	25	25	25	25	25	25
Adenoma Single	3	0	3	3	4	0
Adenoma Multiple	1	24	0	1	0	0
Carcinoma	0	8	0	1	1	0
Number of Males with at Least 1 Type of Lung Tumor	4	25*	3	5	5	0
Females						
Number Examined	25	25	25	25	25	24
Adenoma Single	3	0	1	2	1	0
Adenoma Multiple	0	25	0	0	0	0
Carcinoma	0	24	0	0	0	0
Number of Females with at Least 1 Type of Lung Tumor	3	25*	1	2	1	0
Both Sexes Combined						
Number of Animals with at Least One Type of Tumor	7	50	4	7	6	0

Note: Multiple adenomas and/or carcinomas were present in the same animal in urethane treated mice

* p<0.05 (Fisher's Exact Test) compared to vehicle controls (Group 1).

Splenic hemangiosarcomas were observed in a few animals in most doxepin-treated groups (see the sponsor's summary table 24, following). Splenic hemangiosarcomas are a spontaneous tumor in this strain of mice.

Table 24 - Incidence of Splenic Hemangiosarcoma Tumors in rasH2 Mice

	Vehicle	Urethane 1000 mg/kg/day	Doxepin 25 mg/kg/day	Doxepin 50 mg/kg/day	Doxepin 75 mg/kg/day	Doxepin 100 mg/kg/day
Males						
Number Examined	25	25	25	25	25	25
Hemangiosarcoma	0	23*	4	0	3	3
Females						
Number Examined	25	25	25	25	25	24
Hemangiosarcoma	0	23*	2	1	0	2

Note: Multiple adenomas and/or carcinomas were present in the same animal in urethane treated mice

* p<0.05 (Fisher's Exact Test) compared to vehicle controls (Group 1).

MOUSE STUDY COMMENTS:

There were no statistically significant, dose-related increases in tumors in doxepin-treated animals. The nasal cavity tumors are of note because they are a new finding for (b) (4) and this strain of mice. The splenic hemangiosarcomas are of note because the incidence rate in males, though not dose-dependent, exceeded the historical background rate. These two tumors could be considered for inclusion in the label.

2.6.6.3 Repeat Dose Toxicology

Study title: *SP-D0110: 28-Day Repeated-Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Hybrid Mice With A Preliminary Range-finding Toxicity Study*

Key study findings:

- In 28-day study, MTD = 50 mg/kg (based on moderate clinical signs [e.g., comatose, dyspnea] that resolved); Also “prolonged” clinical signs (@ 100) and mortality (@150) in 5-day
- In 28-day study, sponsor NOAEL = “between 25 & 50 mg/kg/day”

Study no.:

AB37CC.2G3R (b) (4)

Volume #, and page #:

Electronic submission, 325 pgs.

Conducting laboratory and location:

(b) (4)

Date of study initiation:

October 2, 2006

GLP compliance:

Yes, pg. 2

QA report: yes (X) no ()

Pgs. 3-4

Drug, lot #, and % purity:

Doxepin HCl, lot 3045911,
in sterile water for injection, USP

Methods

Doses:

5-Day

0, 10, 25, 50, 100 & 150 mg/kg/day

28-day

0, 10, 25 and 50 mg/kg/day

Species/strain:

CByB6F1 hybrid mice, Tg.rasH2
non-transgenic littermates

Number/sex/group (main study):

5-Day

Main: 5/sex/gp

At initiation, ~8 wks of age;

19.8-32.4 g

28-day

Main: 10/sex/gp

Plus TK: 35/sex/gp & 5/sex/gp con

At initiation, ~7-8 wks of age;

18.7-28.7 g

Route, formulation, volume, and infusion rate: PO, QD by oral gavage, 10 ml/kg

Other details:

ad libitum diet and water

Individually housed in polycarbonate cages

Observations times & Results:

5-Day

Mortality:

There were four Gp6 mortalities. No evidence of gavage error was found in the animals found dead. See the sponsor's summary table, below. All other animals survived until terminal sacrifice.

TABLE 1 - SUMMARY OF MORTALITY

MALES

		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Day 2	Found Dead	0/5	0/5	0/5	0/5	0/5	1/5
Day 3	Found Dead	0/5	0/5	0/5	0/5	0/5	1/5
Day 6	Terminal Sacrifice	5/5	5/5	5/5	5/5	5/5	3/5

FEMALES

		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Day 2	Found Dead	0/5	0/5	0/5	0/5	0/5	2/5
Day 6	Terminal Sacrifice	5/5	5/5	5/5	5/5	5/5	3/5

Note: Represents the number of animals affected / the number of animals started on test.
Statistical analysis (Fisher's Exact Test) did not reveal any significant differences when mortality in Group 6 males was compared to Group 1 males or when mortality in Group 6 females was compared to Group 1 females.

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day
 Group 4 - 50 mg/kg/day Group 5 - 100 mg/kg/day Group 6 - 150 mg/kg/day

Clinical signs:

Dose-related clinical observations noted included coma, lethargy, prostration and labored breathing/dyspnea. These signs first appeared on D1-4 and continued through D5 in most animals. See the sponsor's summary tables below for details. No abnormalities were noted during the detailed hands-on observations in the 5-Day study.

TABLE 2 – SUMMARY OF CLINICAL OBSERVATION INCIDENCE – CAGESIDE (5-DAY)

Clinical Observations - Clinical Signs by Group
 Study : AB37CC.2G3R (b) (4) - 5 Day Range-finding Toxicity Study in CByB6Fl Hybrid

Sex: Male	Day numbers relative to Start Date					
	Group 1 0 mg/kg/day	Group 2 10 mg/kg/day	Group 3 25 mg/kg/day	Group 4 50 mg/kg/day	Group 5 100 mg/kg/day	Group 6 150 mg/kg/day
Comatose						
Number of Observations	.	.	.	11	13	11
Number of Animals	.	.	.	5*	5*	4*
Days from - to	.	.	.	2 4	2 5	2 5
Lethargic						
Number of Observations	.	.	.	7	7	.
Number of Animals	.	.	.	4*	4*	.
Days from - to	.	.	.	4 5	4 5	.
Prostrate						
Number of Observations	.	.	.	9	19	20
Number of Animals	.	.	.	4*	5*	5*
Days from - to	.	.	.	2 4	1 5	1 5
Labored/Dyspnea						
Number of Observations	.	.	.	4	19	20
Number of Animals	.	.	.	2	5*	5*
Days from - to	.	.	.	2 3	1 5	1 5

* p ≤ 0.05 (Dunnett's T-test) when compared to Group 1.

TABLE 2 – SUMMARY OF CLINICAL OBSERVATION INCIDENCE – CAGESIDE (5-DAY CONTINUED)

Clinical Observations - Clinical Signs by Group
 Study : AB37CC.2G3R (b) (4) - 5 Day Range-finding Toxicity Study in CByB6Fl Hybrid

Sex: Female	Day numbers relative to Start Date					
	Group 1 0 mg/kg/day	Group 2 10 mg/kg/day	Group 3 25 mg/kg/day	Group 4 50 mg/kg/day	Group 5 100 mg/kg/day	Group 6 150 mg/kg/day
Comatose						
Number of Observations	.	.	.	8	14	14
Number of Animals	.	.	.	4*	5*	5*
Days from - to	.	.	.	2 3	2 5	2 5
Lethargic						
Number of Observations	.	.	.	9	6	.
Number of Animals	.	.	.	5*	3	.
Days from - to	.	.	.	4 5	4 5	.
Prostrate						
Number of Observations	.	.	.	14	19	19
Number of Animals	.	.	.	5*	5*	5*
Days from - to	.	.	.	1 3	1 5	1 5
Labored/Dyspnea						
Number of Observations	.	.	.	14	19	19
Number of Animals	.	.	.	5*	5*	5*
Days from - to	.	.	.	1 3	1 5	1 5

* p ≤ 0.05 (Dunnett's T-test) when compared to Group 1.

Body weights:

Generally, mean body weights of Gp5 and Gp6 were reduced. Day 5 mean body weights in Gp5 were 11.9% less for males [ss] and 2.5% less for females than corresponding vehicle control group. Day 5 group mean body weights in Gp6 were 10.1% less for males and 8.7% less for females. Body weight gain data demonstrated statistically significant decreases in Gp5 and Gp6. See the sponsor's summary data, below.

TABLE 4 - SUMMARY OF BODY WEIGHTS (5-DAY)

		Body weight (Grams)	

		Day numbers relative to Start Date	
Group	Sex	1	5
1m	Mean	27.86	27.22
	S.D.	0.81	0.88
	N	5	5

2m	Mean	29.08	28.20
	S.D.	3.00	2.95
	N	5	5

3m	Mean	28.18	27.46
	S.D.	1.06	0.73
	N	5	5

4m	Mean	27.44	25.68
	S.D.	1.49	2.23
	N	5	5

5m	Mean	26.28	23.98*
	S.D.	1.36	1.08
	N	5	5

6m	Mean	28.20	24.47
	S.D.	2.19	2.06
	N	5	3

* $p \leq 0.05$ (Dunnett's t-test) when compared to Group 1.

Arithmetic Mean Values Presented

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day
 Group 4 - 50 mg/kg/day Group 5 - 100 mg/kg/day Group 6 - 150 mg/kg/day

TABLE 4 - SUMMARY OF BODY WEIGHTS (5-DAY CONTINUED)

		Body weight (Grams)	

		Day numbers relative to Start Date	
Group	Sex	1	5
1f	Mean	21.60	21.02
	S.D.	1.06	1.01
	N	5	5

2f	Mean	22.10	21.96
	S.D.	1.16	1.04
	N	5	5

3f	Mean	21.30	21.20
	S.D.	0.45	0.48
	N	5	5

4f	Mean	21.62	21.22
	S.D.	1.52	1.31
	N	5	5

5f	Mean	22.26	20.50
	S.D.	1.42	1.43
	N	5	5

6f	Mean	21.26	19.20
	S.D.	1.09	0.78
	N	5	3

Statistical analysis (Dunnett's t-test) did not reveal any significant differences when Groups 2-6 were compared to Group 1.

Arithmetic Mean Values Presented

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day
 Group 4 - 50 mg/kg/day Group 5 - 100 mg/kg/day Group 6 - 150 mg/kg/day

TABLE 5 - SUMMARY OF BODY WEIGHT GAINS (5-DAY)

Body Weight Gain (Grams)

Day numbers relative to Start Date			Abs
Group	Base Weight	From:	Gain
Sex	Day	To:	1
			5
1m	27.86	Mean	-0.64
	0.81	S.D.	0.42
	5	N	5
2m	29.08	Mean	-0.88
	3.00	S.D.	0.42
	5	N	5
3m	28.18	Mean	-0.72
	1.06	S.D.	0.45
	5	N	5
4m	27.44	Mean	-1.76
	1.49	S.D.	1.02
	5	N	5
5m	26.28	Mean	-2.30*
	1.36	S.D.	0.49
	5	N	5
6m	28.20	Mean	-4.27*
	2.19	S.D.	1.70
	5	N	3

* p ≤ 0.05 (Dunnett's t-test) when compared to Group 1.

Abs Gain = absolute body weight gain between base period and end of the analysis period

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day
 Group 4 - 50 mg/kg/day Group 5 - 100 mg/kg/day Group 6 - 150 mg/kg/day

TABLE 5 - SUMMARY OF BODY WEIGHT GAINS (5-DAY CONTINUED)

Body Weight Gain (Grams)

Day numbers relative to Start Date			Abs
Group	Base Weight	From:	Gain
Sex	Day	To:	1
			5
1f	21.60	Mean	-0.58
	1.06	S.D.	0.26
	5	N	5
2f	22.10	Mean	-0.14
	1.16	S.D.	0.42
	5	N	5
3f	21.30	Mean	-0.10
	0.45	S.D.	0.61
	5	N	5
4f	21.62	Mean	-0.40
	1.52	S.D.	0.25
	5	N	5
5f	22.26	Mean	-1.76*
	1.42	S.D.	0.88
	5	N	5
6f	21.26	Mean	-2.40*
	1.09	S.D.	0.87
	5	N	3

* p ≤ 0.05 (Dunnett's t-test) when compared to Group 1.

Abs Gain = absolute body weight gain between base period and end of the analysis period

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day
 Group 4 - 50 mg/kg/day Group 5 - 100 mg/kg/day Group 6 - 150 mg/kg/day

Gross pathology, Organ weights, Histopathology & TK: Not performed

28-Day

Mortality: *Twice daily*

All Main and TK Study animals in the 28-Day study survived until terminal/scheduled sacrifice.

Clinical signs: *once daily (within 2 hours after the last animal was dosed)*

Drug-related clinical observations including coma, decreased motor activity, lethargy, prostration and labored breathing/dyspnea were noted during postdose cageside observations in both sexes. The incidence of these clinical signs was statistically significantly increased in MD and HD animals of both sexes when compared to the vehicle control group; MD and HD animals showed no clinical signs after D20. No abnormal detailed hands-on observations were recorded.

TABLE 7 – SUMMARY OF CLINICAL OBSERVATION INCIDENCE – CAGESIDE (28-DAY)

		Clinical Observations - Clinical Signs by Group			
Study : AB37CC.2G3F (b) (4)		28-Day Repeated Dose Oral Toxicity and Toxicokinetic			
Sex: Male		Day numbers relative to Start Date			
		Group 1	Group 2	Group 3	Group 4
		0 mg/kg/day	10 mg/kg/day	25 mg/kg/day	50 mg/kg/day
Comatose					
Number of Observations	97
Number of Animals	10*
Days from - to	1 12
Decreased Motor Activity					
Number of Observations	8
Number of Animals	8*
Days from - to	13 13
Lethargic					
Number of Observations	.	.	80	69	
Number of Animals	.	.	10*	10*	
Days from - to	.	.	1 12	8 20	
Prostrate					
Number of Observations	97
Number of Animals	10*
Days from - to	1 12
Labored/Dyspnea					
Number of Observations	97
Number of Animals	10*
Days from - to	1 12

* $p \leq 0.05$ (Dunnett's t-Test) when compared to Group 1.

**TABLE 7 – SUMMARY OF CLINICAL OBSERVATION INCIDENCE – CAGESIDE
(28–DAY CONTINUED)**

Clinical Observations - Clinical Signs by Group

Study : AB37CC.2G3R (b) (4) - 28-Day Repeated Dose Oral Toxicity and Toxicokinetic

Day numbers relative to Start Date

Sex: Female

	Group 1 0 mg/kg/day	Group 2 10 mg/kg/day	Group 3 25 mg/kg/day	Group 4 50 mg/kg/day
Comatose				
Number of Observations	.	.	.	73
Number of Animals	.	.	.	10*
Days from - to	.	.	.	1 11
Decreased Motor Activity				
Number of Observations	.	.	.	11
Number of Animals	.	.	.	10*
Days from - to	.	.	.	12 13
Lethargic				
Number of Observations	.	.	82	93
Number of Animals	.	.	10*	10*
Days from - to	.	.	1 11	6 20
Prostrate				
Number of Observations	.	.	.	73
Number of Animals	.	.	.	10*
Days from - to	.	.	.	1 11
Labored/Dyspnea				
Number of Observations	.	.	.	73
Number of Animals	.	.	.	10*
Days from - to	.	.	.	1 11

* p ≤ 0.05 (Dunnett's t-Test) when compared to Group 1.

Body weights: Days 1, 8, 15, 22, 28 (pre-fasted weight) & 29 (terminal fasted weight)
Mean body weights appeared relatively unaffected; however, the sponsor indicated there was a drug-related trend for slightly reduced body weight gains that was more pronounced in the males. See the sponsor's summary table, below.

TABLE 10 – SUMMARY OF BODY WEIGHT GAIN (28-DAY)

Body Weight Gain (Grams)

Group Sex	Base Weight Day 1	From: To:	Day numbers relative to Start Date				Abs Gain
			1 8	8 15	15 22	22 28	
1m	26.00	Mean	0.07	0.00	0.76	-0.34	0.49
	1.87	S.D.	0.72	0.55	0.93	0.31	0.91
	10	N	10	10	10	10	10
2m	26.52	Mean	-0.67	0.12	0.51	-0.32	-0.36
	1.43	S.D.	0.49	0.58	0.39	0.50	1.00
	10	N	10	10	10	10	10
3m	25.88	Mean	-0.47	-0.23	0.40	0.05	-0.25
	1.02	S.D.	0.55	0.76	0.76	0.62	0.79
	10	N	10	10	10	10	10
4m	25.92	Mean	-0.89*	0.49	0.20	-0.31	-0.51
	1.49	S.D.	0.93	0.31	0.51	0.68	0.91
	10	N	10	10	10	10	10
1f	20.82	Mean	-0.01	0.53	0.37	0.58	1.47
	1.07	S.D.	0.87	0.88	0.44	0.47	0.78
	10	N	10	10	10	10	10
2f	20.42	Mean	-0.06	0.99	0.20	0.76	1.89
	0.89	S.D.	0.52	0.46	0.58	0.57	0.83
	10	N	10	10	10	10	10
3f	19.93	Mean	0.19	0.01	-0.06	1.09	1.23
	1.16	S.D.	0.60	0.74	0.69	0.80	1.63
	10	N	10	10	10	10	10
4f	20.46	Mean	0.39	-0.27*	0.20	0.91	1.23
	1.05	S.D.	0.54	0.61	0.60	0.36	0.73
	10	N	10	10	10	10	10

Abs Gain = absolute body weight gain between base period and end of the analysis period

* p ≤ 0.05 (Dunnett's t-test) when compared to Group 1.

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day Group 4 - 50 mg/kg/day

Food consumption: Days 1, 8, 15, 22 & 28

There was an apparent drug-related trend for decreased food consumption that was more pronounced in the males. Total food consumption in the HDM was 7.7% less than controls. Total food consumption in HDF did not appear affected, but weekly consumption values indicated a transient decrease (13.5%, 3.4% and 2.8% less than controls in weeks 2, 3 and 4). See the sponsor's summary data, below.

TABLE 11 - SUMMARY OF FOOD CONSUMPTION (28-DAY STUDY)

Day numbers relative to Start Date

Group	From:	1	8	15	22	Total
Sex	To:	8	15	22	28	28
1m	Mean	5.31	4.49	4.47	4.03	124.1
	S.D.	1.25	0.81	1.24	0.93	16.8
	N	10	10	10	10	10
2m	Mean	5.29	4.96	5.33	4.70	116.8
	S.D.	1.98	0.76	1.55	0.88	38.1
	N	8	10	8	8	10
3m	Mean	5.71	4.89	5.12	4.41	116.2
	S.D.	1.37	1.36	1.32	0.72	23.1
	N	8	9	9	8	10
4m	Mean	5.23	4.31	3.88	3.79	114.5
	S.D.	2.16	0.93	1.14	1.08	22.9
	N	10	10	10	9	10
1f	Mean	4.34	4.59	5.05	4.64	92.0
	S.D.	0.39	1.62	1.41	1.04	33.1
	N	6	7	9	7	10
2f	Mean	5.47	5.10	4.45	4.54	125.4*
	S.D.	1.32	1.51	1.03	1.71	24.5
	N	9	10	9	10	10
3f	Mean	5.08	5.67	4.72	3.73	98.4
	S.D.	0.72	1.06	1.26	0.89	31.7
	N	8	7	8	7	10
4f	Mean	4.94	3.97	4.88	4.51	114.7
	S.D.	0.93	1.24	1.18	1.64	19.8
	N	10	9	9	9	10

NOTE: In Groups with N values less than 10, there were animals with invalid food consumption values that were excluded from weekly data as per (b) (4) SOPs. See individual food consumption data in Appendix C.

*p ≤ 0.05 (Dunnett's t-test) when compared to Group 1.

Arithmetic Mean Values Presented

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 25 mg/kg/day Group 4 - 50 mg/kg/day

Hematology: At termination (Day 29), retro-orbital sinus bleed

Main study animals were fasted overnight, anesthetized with CO₂/O₂ and bled from the retro-orbital sinus for clinical pathology samples on D29. Whole blood samples for hematology from up to 5 animals/sex/group were prepared. All apparent changes were considered incidental by the Clinical Pathologist. WBC appeared decreased in MDM (43%) and HDM (47%). Segmented neutrophils (up to 30%), lymphocytes (up to 55%) and monocytes (up to 86%) appeared decreased in MD and HD M. WBC appeared decreased in HDF (22%), but were variable.

Clinical chemistry: At termination (Day 29), retro-orbital sinus bleed

Main study animals were fasted overnight, anesthetized with CO₂/O₂ and bled from the retro-orbital sinus for clinical pathology samples on D29. Serum samples for clinical chemistry from up to 5 animals/sex/group were prepared. All changes were considered incidental by the Clinical Pathologist. Total bilirubin showed a dose-related slight reduction in HDF (as much as 31%).

Gross pathology: At termination (Day 29)

There were no gross lesions in this study.

Organ weights: At termination (Day 29)

The sponsor recorded no organ weight changes in this study; there were no statistically significant changes. Absolute and relative adrenal weights appeared to show a dose-related decrease, with HDM reduced 23% and 20%, respectively. Absolute and relative adrenal weights also appeared slightly reduced in HDF (13% and 10%, respectively). Absolute and relative ovary weights appeared slightly reduced in HDF (14% and 12%, respectively).

Histopathology: Adequate Battery: yes (X), no ()

Peer review: yes (), no (X)

Tissues from the vehicle control and HD group were embedded in paraffin and sectioned at ≤ 6 microns, stained with H&E and evaluated microscopically. The sponsor recorded no drug-related histopathological changes in this study. One HDF showed minimal, focal, granulomatous inflammatory foreign body reaction in the nasal cavity.

Toxicokinetics: from 3/sex/dose/time point, D28 at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 & 24 hours postdose Plasma concentrations for doxepin and nordoxepin were variable. Absorption was rapid, and terminal half-life increased with dose. C_{max} and AUC showed greater than dose-proportional increases. See the sponsor's summary table, below.

Summary of Doxepin and Nordoxepin Plasma Toxicokinetic Parameters on Day 28 of Daily Oral Administration of Doxepin HCl to Mice

Group	Dosage (mg/kg/day) ^a	Gender	C_{max} (ng/mL)	t_{max} (h)	t_{last} (h)	AUC_{last} (ng·h/mL)	AUC (ng·h/mL)	$t_{1/2}$ (h)
Doxepin								
2	10	M	46.3	0.25	4	55.0	58.4	1.0
		F	25.8	0.25	3	33.4	36.8	0.93
3	25	M	165	0.25	12	267	287	5.7
		F	166	0.25	8	174	183	2.4
4	50	M	406	0.25	24	735	743	4.0
		F	464	0.25	24	655	665	7.1
Nordoxepin								
2	10	M	55.0	0.25	6	90.0	92.8	1.1
		F	13.9	0.5	3	19.5	22.8	0.98
3	25	M	234	0.25	12	545	614	6.2
		F	63.1	0.25	8	121	NE	NE
4	50	M	658	0.5	24	3330	3410	4.1
		F	295	0.5	24	751	787	7.8

NE: Not estimated, due to insufficient characterization of terminal phase.

a: Doxepin HCl dosage.

2.6.6.4 Genetic Toxicology

Genetic toxicology studies will not be reviewed here. Please see the P/T review dated 2/2/07 for I67,162 submissions N046 & N048, dated 9/15/06 and 2/2/07 (finalized study reports were submitted SN054, dated 4/2/07). A standard battery of genetic toxicology

studies (i.e., *in vitro* bacterial reverse mutation assay, *in vitro* chromosomal aberrations assay (HPBL) and *in vivo* rat micronucleus assay) were conducted, and were negative.

2.6.6.5 Carcinogenicity

Study title: *SP-D0111: 26-WEEK REPEATED DOSE ORAL CARCINOGENICITY STUDY IN Tg.rasH2 MICE*

Key study findings:

- **Non-statistically significant increases in nasal cavity, lung and spleen tumors**
- **Nasal lesions and tumors are not a background lesion in this strain**
- **Lung and spleen tumors are spontaneous tumors in this strain**

Evaluation of tumor findings:

According to the FDA statistical reviewer (Dr. M.A. Rahman, review dated 6/30/2008), no significant positive dose-response relationships in tumor incidence were detected in males or females.

Study no.:

AB37CC.7G8R (b) (4)

Volume #, and page #:

Electronic submission, 877 pages

Conducting laboratory and location:

(b) (4)

Date of study initiation:

April 16, 2007

GLP compliance:

Yes

QA report: yes (X) no ()

Drug, lot #, and % purity:

Doxepin HCl, Lot 3045911, 100.0%

(b) (4) E-isomer; (b) (4) Z-isomer

In Sterile Water for Injection, USP Grade

CAC concurrence:

Dose selection-No; Study results- [pending]

Methods

Doses:

0, 25, 50, 75 and 100 mg/kg doxepin HCl

Basis of dose selection:

MTD in 5- & 28-day toxicity study in

CByB6F1 Hybrid mice

Positive Control:

Urethane (in sterile saline), 1000 mg/kg

Species/strain:

Tg.rasH2 mice, [CB6F1Jic- TgrasH2@Tac] (hemizygous C57BL/6 x BALB/cBy knock-in mouse carrying the human prototype c-Ha-ras gene with its own promoter/enhancer) (b) (4)

Number/sex/group (main study):

(see sponsor's summary table, below)

Table 6 – Experimental Design for Carcinogenicity and Toxicokinetics of Doxepin HCl in Mice

Dose Group and Treatment	Number of Animals			
	Main Study (Tg.rasH2)		TK Study (CByB6F1)	
	Male	Female	Male	Female
<u>Group 1</u> Vehicle Control	25	25	5	5
<u>Group 2</u> Positive Control, urethane*	25	25	-	-
<u>Group 3</u> Low dose (25 mg/kg/day)	25	25	35	35
<u>Group 4</u> Middle dose (50 mg/kg/day)	25	25	35	35
<u>Group 5</u> Middle High dose (75 mg/kg/day)	25	25	35	35
<u>Group 6</u> High dose (100 mg/kg/day)	25	25	35	35
Total	150	150	145	145

*The Positive Control animals were administered a total of 3 intraperitoneal injections of urethane (1000 mg/kg) on Days 1, 3, and 5.

Route, formulation, volume:

Frequency of dosing:

Satellite groups for toxicokinetics:

Age:

Animal housing:

Dietary parameters:

Drug stability/homogeneity:

Deviations from study protocol:

PO, by oral gavage, vol.= 10 ml/kg

doxepin QD for 182 days

(for urethane POS CON, 3 IP injection)

CByB6F1 Hybrid mice (Tg.rasH2 non-transgenic littermates)

TK: (b) (4)

Main: 8-9 weeks; TK: 9-10 weeks

Individually housed

ad libitum diet & water

Not performed- previous data

Study Protocol:

1) animals were single-housed during quarantine because they had been mixed at receipt and had to be genotyped

2) 1HDF was removed from study because she was the incorrect strain

3) labels on tail snip samples were not marked

Methodological Notes:

Positive control animals were sacrificed as a group (on D116 and D114 in the males and females, respectively) once signs of toxicity were evident in the majority of animals.

This was done to avoid the loss of tissues for histopathologic evaluation due to autolysis.

The primary target organs for urethane (used as the positive control article for this study) are lungs and spleen; therefore, the expected urethane-related clinical signs include: rapid and shallow breathing, palpable internal masses, and edema.

Observation times & Results

Mortality: *Twice daily*

In the main study, early mortality (found dead or sacrificed moribund) was observed in a few control and doxepin-treated animals, and in a number of positive controls. FDA statistical review (see review by Dr. Rahman) indicated that mortality was not significantly increased in doxepin-treated groups and was significantly increased in the urethane-treated groups. Early mortality was observed in 3/25 CONF, 1/25 LDF, 1/25 MDF, 2/25 MHDF, 1/25 LDM, 3/25 HDM. A slight increase in early mortality was suggested in HDM compared to CONM, and appeared to be supported by the early mortalities demonstrated in the HDTK M. In the TK portion of the study, 1/35 MDF (D102), 2/35 MHDM, and 7/35 HDM died early. No increase in mortality was apparent in females. See the sponsor's summary tables 8 and 9, next pages. The cause of death, if known, is also provided for the main study animals. There was no evidence of gavage error in any of the animals that died early.

Table 8 - SUMMARY OF MORTALITY (MAIN STUDY Tg.rasH2 ANIMALS)

		MALES						
		COD	Group 1	Group 2*	Group 3	Group 4	Group 5	Group 6
Day 6	Found Dead	U	-	1/25	-	-	-	-
Day 63	Found Dead	P	-	1/25	-	-	-	-
Day 71	Found Dead	U	-	-	-	-	-	1/25
Day 75	Found Dead	P	-	1/25	-	-	-	-
Day 84	Found Dead	P	-	2/25	-	-	-	-
Day 96	Found Dead	P	-	1/25	-	-	-	-
Day 98	Found Dead	P	-	1/25	-	-	-	-
Day 103	Found Dead	P	-	1/25	-	-	-	-
Day 109	Found Dead	U	-	-	-	-	-	1/25
Day 114	Found Dead	P	-	1/25	-	-	-	-
Day 115	Found Dead	P	-	1/25	-	-	-	-
Day 141	Found Dead	U	-	-	1/25	-	-	-
Day 155	Found Dead	Hs	-	-	-	-	-	1/25
Day 116	Scheduled Sacrifice	NA	-	15/25	-	-	-	-
Day 183 or 184	Terminal Sacrifice	NA	25/25	-	24/25	25/25	25/25	22/25
TOTAL:			25/25	25/25	25/25	25/25	25/25	25/25

		FEMALES						
		COD	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Day 17	Found Dead	U	-	-	-	-	-	1/25
Day 91	Found Dead	U	-	-	1/25	-	-	-
Day 95	Found Dead	P	-	1/25	-	-	-	-
Day 96	Found Dead	P	-	2/25	-	-	-	-
Day 100	Other ¹	NA	-	-	-	-	-	1/25
Day 102	Found Dead	P	-	1/25	-	-	-	-
Day 104	Found Dead	P	-	1/25	-	-	-	-
Day 105	Found Dead	P	-	1/25	-	-	-	-
Day 120	Moribund Sacrifice	Pv	-	-	-	-	-	1/25
Day 125	Found Dead	U	1/25	-	-	-	-	-
Day 126	Found Dead	U	-	-	-	-	1/25	-
Day 156	Found Dead	U	-	-	-	-	1/25	-
Day 174	Found Dead	U	-	-	-	1/25	-	-
Day 176	Found Dead	L	1/25	-	-	-	-	-
Day 182	Found Dead	HeAl	1/25	-	-	-	-	-
Day 114	Scheduled Sacrifice	NA	-	19/25	-	-	-	-
Day 183 or 184	Terminal Sacrifice	NA	22/25	-	24/25	24/25	23/25	22/25
TOTAL:			25/25	25/25	25/25	25/25	25/25	25/25

¹ Genotyping results revealed that Group 6 female 6276 was the wrong strain, therefore this animal was sacrificed and all associated data was removed from the study.

Note: Represents the number of animals affected / the number of animals started on test.

* p< 0.05 (Fisher's Exact Test) compared to Group 1.

COD = Cause of Death NA = Not Applicable

U = Undetermined L = Lymphoma (spleen, liver) HeAl = Hemangiosarcoma (ear), Adenoma, lung

P = Positive Control-related death Hs = Hemangiosarcoma (spleen) Pv = Papilloma (vagina)

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - Positive Control Group 3 - 25 mg/kg/day

Group 4 - 50 mg/kg/day Group 5 - 75 mg/kg/day Group 6 - 100 mg/kg/day

Cageside Observations

	MALES						FEMALES					
	0	POS	LD	MD	MHD	HD	0	POS	LD	MD	MHD	HD
Comatose												
# obs				23	20	28					8	27
# animals				23*	20*	17*					8*	24*
Days from-to				1	1	1 8					1	1 8
Lethargic												
# obs		25		19	141	79		26		68	157	49
# animals		25*		14*	25*	23*		25*		25*	25*	19*
Days from-to		1		1 183	1 176	1 176		1 8		1 141	1 141	8 148
Dec Activity												
# obs				1		222					32	296
# animals				1		25*					13*	23*
Days from-to				176		36 176					106 134	43 141
Labored / Dyspnea												
# obs				7	4	7						
# animals				5	4	7*						
Days from-to				176 183	176	176						
Rapid / Shallow												
# obs			3	12	2	3						
# animals			2	3	1	3						
Days from-to			176 183	134 183	176 183	176						

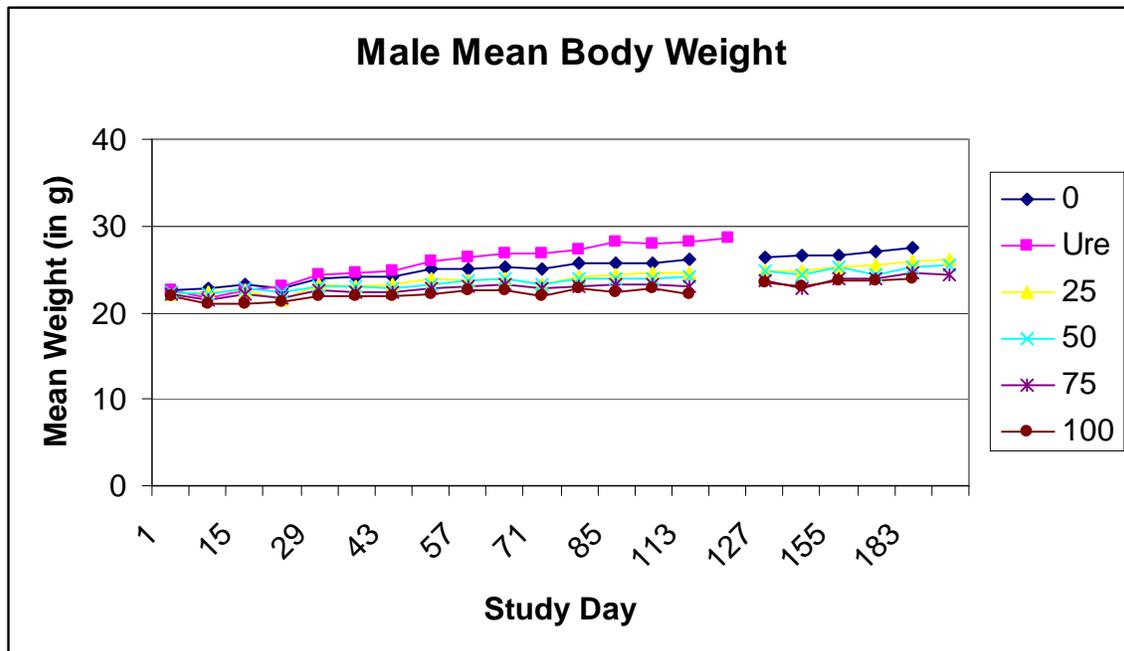
Hands-on Observations

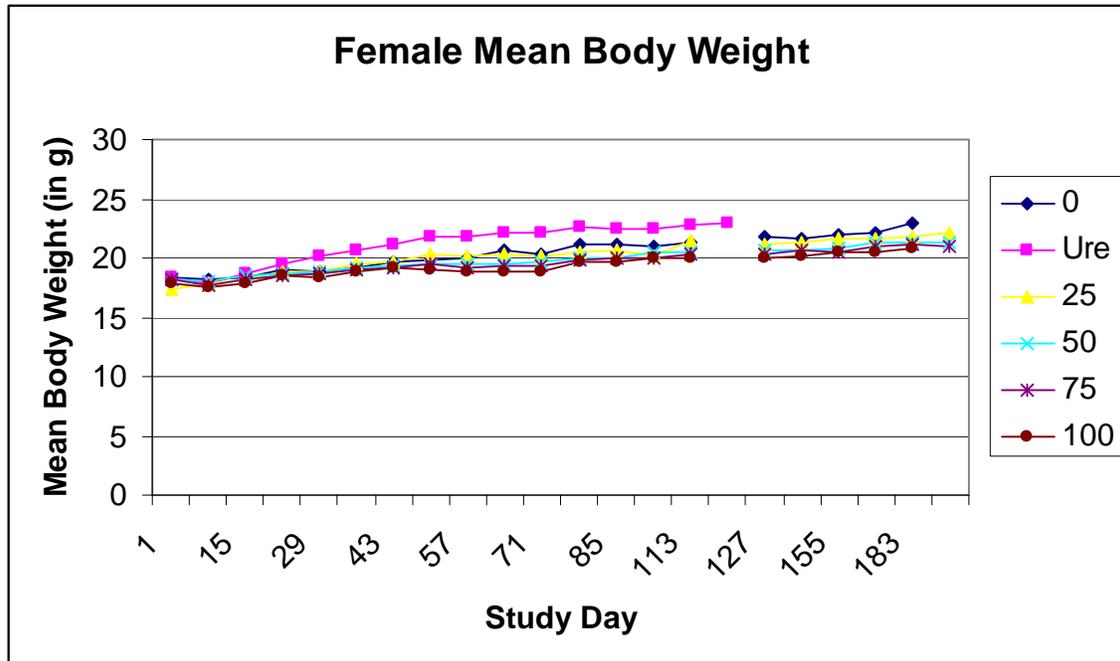
	MALES						FEMALES					
	0	POS	LD	MD	MHD	HD	0	POS	LD	MD	MHD	HD
Rapid & Shallow												
# obs		118	1	20	11	56	16	121	10	26	24	82
# animals		21*	1	10*	9*	21*	1	23*	2	15*	16*	20*
Days from-to		78 116	184	64 184	176 184	127 183	78 183	71 114	134 184	183 184	183 184	141 183
Labored / Dyspnea												
# obs		1		3		2		1				
# animals		1		1		1		1				
Days from-to		78		176 184		176 183		99				
Mass												
# obs								9				16
# animals								2				1
Days from-to								78 114				15 120
Discharge												
# obs							1		2	3		22
# animals							1		1	1		2
Days from-to							183		183 184	176 184		15 176

* p < 0.05, Fisher's Exact test, compared to CON

Body weights: *Weekly through Week 13 and biweekly thereafter*

Group mean body weights were slightly but statistically significantly and dose-dependently reduced in all doxepin-treated groups, compared to controls. Mean body weight reductions were statistically significant in MHDM and HDM beginning week 2, and in LDM and MDM beginning week 6. The decreases in mean body weights in the LD, MD, MHD and HD male doxepin-treated groups on Day 183 were 6.2%, 8.4%, 10.9% and 13.2% less than the vehicle control, respectively. Statistically significant reductions in group mean body weight in females were not as consistent as those observed in males, but were generally reduced after week 10. The HDF, MHDF, MDF and LDF generally showed reductions beginning approximately week 8, week 9, week 10 and week 27 (respectively). The decreases in mean body weights in the LD, MD, MHD and HD female doxepin-treated groups on Day 183 were 5.1%, 7.4%, 8.1% and 9.3% less than the vehicle control. See the reviewer's figures, below.





Weekly body weight gain in the doxepin-treated groups in both sexes was sporadically statistically significantly lower than the vehicle control group; however, the absolute body weight gain (from Day 1 to Day 183) was statistically significantly and dose-dependently decreased in MD, MHD and HD in both sexes when compared to vehicle controls. LD animals also showed a decrease in absolute body weight gain [nss]. Group mean absolute weight gain decreases ranged from 21.3% to 56.9% less than the vehicle control in doxepin-treated males, and from 5.8% to 38.1% less than the vehicle control in the doxepin-treated females.

Food consumption:

There were few significant differences in weekly group mean food consumption in the doxepin treatment groups compared to the vehicle control group; however, total food consumption (from Day 1 to Day 183) was statistically significantly and dose-dependently decreased in MDM, MHDM, MHDF, HDM and HDF compared to vehicle controls. Although the differences were not statistically significant, total food consumption in the LDM, LDF and MDF were also lower than that of the vehicle control group. Group mean total food consumption decreases ranged from 3.4% to 14.4% lower than the vehicle control group in the doxepin-treated males, and ranged from 5.7% to 20.7% lower than the vehicle control in the doxepin-treated females.

Organ Weight: *Terminal sacrifice*

The sponsor identified no statistically significant differences in absolute or relative organ weights in doxepin-treated groups of either sex, compared to the vehicle control groups. In males, there appeared to be slight reductions in spleen weights (absolute and relative, HD, 23%) and kidney weights (absolute & relative, dose-related, up to 13%). In females, there appeared to be slight reductions in ovary weights (absolute and relative, dose-related, up to 19%), spleen weights (absolute and relative, \geq MD, up to 22%), kidney

weights (absolute and relative, \geq MD, up to 13%) and heart weights (absolute and relative, dose-related, up to 11%).

Gross pathology: *Terminal sacrifice & early mortalities as needed*

In the doxepin-treated groups, nodules or masses were observed in the spleens of 0/25 CONM, 4/25 LDM, 3/25 MHDM, 3/25 HDM and 0/25 CONF, 1/25 LDF and 3/24 HDF. These lesions were considered to be doxepin-related. Other gross lesions were noted to occur in individual animals, but did not appear drug-related.

In the urethane-treated positive control group (M & F), the expected pulmonary and splenic lesions (i.e., nodules) were noted. Red fluid was observed in multiple body cavities. Thymus was enlarged in 2/25 F. Other lesions were noted to occur in individual animals, but were not clearly urethane-related.

Histopathology: Peer review: yes (), no (X) *Terminal sacrifice*

All tissues collected at necropsy from all groups and selected tissues from the positive control animals (lungs and spleen, and any gross lesions) were embedded, sectioned at ≤ 6 μm , stained with H&E, and evaluated microscopically.

Non-neoplastic:

In the doxepin-treated animals, a number of histopathological alterations were observed; the majority of these alterations were considered spontaneous or incidental by the pathologist.

Microscopic evaluation demonstrated irritation of the nasal cavities, of varying degrees, in control and drug-treated groups. Although nasal cavity lesions were noted in controls as well as doxepin-treated animals, the nature of the irritation was different. In vehicle control animals, the lesion was diagnosed as “an acute inflammatory lesion of the submucosal glands of minimal intensity.” The lesion was described as a few scattered submucosal glands in the nasal cavities of control mice that contained necrotic debris and degenerate neutrophils; the incidence of this lesion was 7/25 and 13/25 in the male and female control mice, respectively. The pathologist considered the alteration a background or spontaneous lesion; notably, the pathologist also stated that nasal cavity lesions have not been previously observed in other vehicle-treated rasH2 mice at (b) (4). The cause of the lesion is unknown. Chronic-active inflammatory, hyperplastic and neoplastic lesions were noted in the nasal cavities of the doxepin-treated groups in both sexes; other than a minimal chronic-active inflammatory lesion observed in 1 control female, these more severe lesions were not noted in the vehicle control groups. See the sponsor’s summary table 25 for details. The sponsor considered the development of inflammation, hyperplasia and metaplasia of the nasal cavities doxepin-related.

Other lesions were noted (e.g., proteinosis in the kidney, hyperplasia of the non-glandular stomach, atypical histiocytic hyperplasia of the thymus, mild myeloid hyperplasia of the bone marrow, submucosal vascular proliferation of the urinary bladder), but were not considered doxepin-related due to the low incidence and/or lack of

dose-response. Inadequate tissue for assessment of pituitary gland was observed in single animals in many groups.

Neoplastic:

In the doxepin-treated animals, possibly drug-related neoplastic alterations were observed in the nasal cavity, the lung and the spleen. A few other neoplastic lesions were observed, but were considered spontaneous or background due to their low incidence and/or lack of dose-dependency.

In addition to the chronic-active inflammation noted in the nasal cavity of doxepin-treated animals, hyperplastic and neoplastic lesions (adenocarcinomas) were noted in the nasal cavities in both sexes that were not noted in the vehicle control groups. Adenocarcinomas were noted in LDM, LDF, MDF and MHDF. See the sponsor's summary table 25 for details. The sponsor hypothesized that the initial local irritation may have led to chronic-active inflammation, subsequently to hyperplasia, and eventually to carcinoma; however, this study was not designed to assess for such a progression. The sponsor considered the development of carcinomas in the nasal cavities noteworthy, as nasal cavity adenocarcinoma did not occur in any vehicle control animal in either sex and is not a spontaneous tumor of Tg.rasH2 mice. However, the sponsor indicated that the development of nasal cavity adenocarcinomas was not "dose- or exposure-related," and that the incidence was not statistically significantly different compared to the vehicle control.

Table 25 - Incidence of Microscopic Nasal Cavity Lesions in rasH2 Mice

	Vehicle	Doxepin 25 mg/kg/day	Doxepin 50 mg/kg/day	Doxepin 75 mg/kg/day	Doxepin 100 mg/kg/day
Males					
Number Examined	25	25	25	25	25
Chronic-Active Inflammation					
Minimal	0	16	14	18	18
Mild	0	0	2	2	6
Moderate	0	0	6	4	0
Submucosal Gland Hyperplasia					
Minimal	0	15	7	8	16
Mild	0	8	16	14	7
Moderate	0	0	1	2	2
Squamous Metaplasia with Hyperplasia					
Minimal	0	21	19	23	23
Mild	0	2	2	1	2
Moderate	0	0	3	0	0
Adenocarcinoma					
	0	2	0	0	0
Females					
Number Examined	25	25	25	25	24
Chronic-Active Inflammation					
Minimal	1	12	14	12	5
Mild	0	1	2	9	9
Moderate	0	0	4	3	8
Submucosal Gland Hyperplasia					
Minimal	0	15	8	6	9
Mild	0	5	10	13	11
Moderate	0	0	4	5	2
Squamous Metaplasia with Hyperplasia					
Minimal	0	13	15	20	19
Mild	0	4	5	3	2
Moderate	0	0	2	1	1
Adenocarcinoma					
	0	1	2	1	0

Note: Multiple adenomas and/or carcinomas were present in the same animal in urethane treated mice
 * p<0.05 (Fisher's Exact Test) compared to vehicle controls (Group 1).

Adenomas and/or carcinomas of the lung were observed in all groups. Pulmonary tumors are spontaneous tumors known to occur in this strain of mouse. The sponsor indicated that statistical analysis revealed no significant increase in incidence in doxepin-treated groups and no relationship to dose or exposure; the FDA statistical reviewer concurred. The incidences of single and/or multiple pulmonary adenomas were similar across the vehicle and doxepin-treated groups. Notably, pulmonary carcinomas were observed in 1MDM and 1MHDM, but were not noted in vehicle control groups of either sex. The

historical control data provided show an average incidence for lung carcinoma of 2% in males in previous studies (N=4; range 0-8%). Based on the overall low and similar incidence of pulmonary tumors in the vehicle- and doxepin-treated groups, as well as the lack of dose dependence, these tumors were not considered drug-related by the sponsor. See the sponsor's summary table 23, below.

Table 23 - Incidence of Pulmonary Tumors in rasH2 Mice

	Vehicle	Urethane 1000 mg/kg/day	Doxepin 25 mg/kg/day	Doxepin 50 mg/kg/day	Doxepin 75 mg/kg/day	Doxepin 100 mg/kg/day
Males						
Number Examined	25	25	25	25	25	25
Adenoma Single	3	0	3	3	4	0
Adenoma Multiple	1	24	0	1	0	0
Carcinoma	0	8	0	1	1	0
Number of Males with at Least 1 Type of Lung Tumor	4	25*	3	5	5	0
Females						
Number Examined	25	25	25	25	25	24
Adenoma Single	3	0	1	2	1	0
Adenoma Multiple	0	25	0	0	0	0
Carcinoma	0	24	0	0	0	0
Number of Females with at Least 1 Type of Lung Tumor	3	25*	1	2	1	0
Both Sexes Combined						
Number of Animals with at Least One Type of Tumor	7	50	4	7	6	0

Note: Multiple adenomas and/or carcinomas were present in the same animal in urethane treated mice

* p<0.05 (Fisher's Exact Test) compared to vehicle controls (Group 1).

Splenic hemangiosarcomas were observed in a few animals in most doxepin-treated groups (see the sponsor's summary table 24, following). The sponsor stated that although splenic hemangiosarcomas were not observed in this study in the vehicle control group of either sex, previous studies conducted with these mice using similar designs at (b) (4) have demonstrated splenic hemangiosarcomas in approximately 3% of male and 5% of female controls (N=4; ranges: 0-4% in males and 0-8% in females). Notably, and as discussed by the FDA statistical reviewer, the incidences observed in this study ranged from 0-16% in the doxepin-treated males and from 0-8% in doxepin-treated females. However, the sponsor's statistical analysis revealed no significant increase in incidence in the doxepin-treated groups compared to controls, and no relationship to dose. The FDA statistical reviewer concurred.

Table 24 - Incidence of Splenic Hemangiosarcoma Tumors in rasH2 Mice

	Vehicle	Urethane 1000 mg/kg/day	Doxepin 25 mg/kg/day	Doxepin 50 mg/kg/day	Doxepin 75 mg/kg/day	Doxepin 100 mg/kg/day
Males						
Number Examined	25	25	25	25	25	25
Hemangiosarcoma	0	23*	4	0	3	3
Females						
Number Examined	25	25	25	25	25	24
Hemangiosarcoma	0	23*	2	1	0	2

Note: Multiple adenomas and/or carcinomas were present in the same animal in urethane treated mice

* p<0.05 (Fisher's Exact Test) compared to vehicle controls (Group 1).

As expected, the urethane-treated positive control mice of both sexes had statistically significantly higher incidences of pulmonary tumors (i.e., multiple adenomas and carcinomas) and splenic hemangiosarcomas when compared with the vehicle control group. Lung tumors were observed in 25/25 mice of both sexes and splenic hemangiosarcomas were observed in 23/25 animals of both sexes. Other tumors were also observed in the urethane-treated mice. Squamous cell carcinoma of the spleen (1M) and squamous cell carcinoma of the stomach (3M & 2F) were also observed. Carcinoma of the nose was observed in 1M.

Toxicokinetics: Wk26 on D177/178 at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 & 24 hrs postdose; 3/sex/dose/time. Animals were bled from the retro-orbital sinus; plasma was shipped overnight on dry ice. Plasma concentrations for doxepin and nordoxepin were variable (i.e., standard deviations were large). See the sponsor's summary tables, below.

Summary of Doxepin and Nordoxepin Data

Group	Dosage ^a (mg/kg/day)	Gender	C _{max} (ng/mL)	t _{max} (h)	t _{last} (h)	AUC _{last} (ng·h/mL)	AUC (ng·h/mL)	t _{1/2} (h)
Doxepin								
3	25	M	162	0.25	12	265	269	2.3
		F	93.9	0.25	8	103	107	2.2
4	50	M	426	0.25	12	866	905	4.5
		F	179	0.5	12	251	262	3.2
5	75	M	531	0.5	24	1210	1330	10.8
		F	450	0.5	24	635	649	5.3
6	100	M	525	0.5	24	1670	1840	9.0
		F	460	0.5	12	903	922	2.0
Nordoxepin								
3	25	M	272	0.25	12	535	547	2.4
		F	145	0.25	8	120	124	2.2
4	50	M	591	0.25	24	1900	1940	4.7
		F	209	0.5	12	424	455	3.3
5	75	M	1160	0.5	24	5660	6720	10.4
		F	818	0.5	24	2200	2230	3.5
6	100	M	1230	0.5	24	12000	14700	9.7
		F	1040	0.5	24	4060	4080	3.0

a: Daily dosage of Doxepin HCl.

Table 7 Ratios of Toxicokinetic Parameters (Nordoxepin:Doxepin) on Week 26 During Daily Oral (Gavage) Administration of Doxepin HCl to Mice

Parameter ^a	25 mg/kg/day (Group 3)		50 mg/kg/day (Group 4)		75 mg/kg/day (Group 5)		100 mg/kg/day (Group 6)	
	Males	Females	Males	Females	Males	Females	Males	Females
C _{max}	1.68	1.54	1.39	1.17	2.18	1.82	2.34	2.26
AUC _{last}	2.02	1.17	2.19	1.69	4.68	3.46	7.19	4.50

a: Ratios are based on mass.

Histopathology inventory

Study	D0110	D0111
Species	Mouse CON&HD	Tg rasH2 Mouse
Adrenals	X	X*
Aorta	X	X
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix		
Colon	X	X
Duodenum	X	X
Epididymis	X	X
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder	X	X
Gross lesions	X	X
Harderian gland	X	X
Heart	X*	X*
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland		
Larynx		
Liver	X*	X*
Lungs	X	X
Lymph nodes, cervical		
Lymph nodes mandibular	X	X
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity	X	X
Optic nerves		
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X	X
Peripheral nerve		
Pharynx		
Pituitary	X	X
Prostate	X	X
Rectum	X	X
Salivary gland	X	X
Sciatic nerve	X	X
Seminal vesicles	X	X
Skeletal muscle	X	X
Skin	X	
Spinal cord	X	X
Spleen	X	X*

Sternum	X	X
Stomach	X	X
Testes	X*	X*
Thymus	X	X
Thyroid	X	X
Tongue		
Trachea	X	X
Urinary bladder	X	X
Uterus	X	X
Vagina	X	X
Zymbal gland		

X, histopathology performed
 *, organ weight obtained

Note: D0111: Only lungs, spleen and gross lesions from urethane-treated positive control

EVALUATION:

The study generally appears adequate (e.g., sensitivity of the assay was demonstrated by the development of pulmonary and splenic tumors in urethane-treated mice), although the health of the animals is somewhat in question due to the atypical nasal cavity findings. While nasal, pulmonary and splenic tumors were observed in doxepin-treated animals, there were no statistically significant, dose-related increases in tumors. The nasal cavity tumors are of note because they are a new finding for (b) (4) and this strain of mice. The increased severity of the inflammatory lesion observed and development of neoplasias in doxepin-treated animals was considered drug-related and of potential relevance. The incidence of the nasal neoplasias was not dose-dependent, but these were rare tumors not previously demonstrated in other similar studies (N=4, historical control data). It is not clear whether there would be any relevance to humans. If the tumors are related to exacerbation of irritation from aspiration of the gavaged dose as the sponsor hypothesized, then it is unlikely that the nasal cavity findings would be relevant for the tablet human dose form. The splenic hemangiosarcomas in males are of note because the incidence rate, though not clearly dose-dependent, exceeded the historical background rate (and range) for (b) (4). Based on these facts, these two tumors could be considered for inclusion in the label.

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/s/

Melissa Banks
2/25/2009 07:50:12 PM
PHARMACOLOGIST

Lois Freed
2/26/2009 09:45:59 AM
PHARMACOLOGIST

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: September 2, 2008

TO: Cathleen Michaloski, Regulatory Health Project Manager
June Cai, M. D., Medical Officer
Division of Neurology Drug Products.

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-036

APPLICANT: Somaxon Pharmaceuticals, Inc..

DRUG: Doxepin Hydrochloride (Silenor)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: New treatment for Insomnia

CONSULTATION REQUEST DATE: March 12, 2008

DIVISION ACTION GOAL DATE: October 1, 2008

PDUFA DATE: December 1, 2008

I. BACKGROUND:

The review division requested inspection of three protocols SP-0501: "A phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy and safety of Doxepin HCL in primary insomnia patients with maintenance difficulties"; protocol SP-0503: "A phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the long-term efficacy and safety of Doxepin HCL, in primary elderly insomnia patients with sleep maintenance

difficulties; and protocol SP-0509 “ A phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter, outpatient study to assess the efficacy and safety of doxepin HCL in elderly patients with primary sleep maintenance insomnia” of the investigational drug doxepin hydrochloride (Silenor), performed for Somaxon Pharmaceuticals, Inc. The sponsor submitted results from the three protocols in support of NDA 22-036.

The primary objective of the study protocol SP0501 was to to evaluate the sedative efficacy of two dose levels (3 and 6mg) of doxepin HCL relative to placebo in the treatment of primary sleep maintenance insomnia: for study protocol SP-0503 was to evaluate the sleep efficacy of two dose levels of doxepin HCL relative to placebo in elderly patients with primary insomnia; and for protocol SP-0509 was to evaluate the efficacy of doxepin HCL 6 mg when administered nightly for up to four weeks in elderly patients. The inspection targeted three domestic clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol	Inspection Dates	Final Classification
Martin B. Scharf, Ph.D. Cincinnati, OH Site # 6	SP-0501	4/8-18/08	NAI
Steven G. Hull, M.D. Overland Park, KS Site # 3	SP-0503	4/6/08	NAI
Issac Marcadis, M.D. West Palm Beach, FL Site # 68	Sp0509	5/12-15/08	NAI

Key to Classifications

NAI = No deviation from regulations

VAI = deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol SP-0501

1. Martin B. Scharf, Ph.D.
Director
The Tri-State Sleep Disorder Center
1275 E. Kemper Road
Cincinnati, Ohio 45246

At this site a total of 110 subjects were screened, 22 subjects were enrolled and 3 subjects were discontinued. Nineteen subjects completed the study. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study. The medical records for 10 subjects enrolled were reviewed in depth including drug accountability records and compared source document to case report forms and data listings for primary efficacy endpoint and adverse events.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection. The data appear acceptable in support of the pending application.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol SP-0503

2. Steven G. Hull, M.D.
Vince & Associates Clinical Research
10103 Metcalf Avenue
Overland Park, Kansas 66212

At this site a total of 70 subjects were screened, 28 subjects were enrolled and 3 subjects were withdraw/discontinued. Twenty five subjects completed the study. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study. The medical records for 14 subjects were reviewed in depth including drug accountability records and compared to case report forms and data listings for primary efficacy endpoint and adverse events.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol SP-0509

3. Issac Marcadis, M.D.
Palm Beach Research Center
1897 Palm Beach Lakes Boulevard, Suite 120
West Palm Beach, Florida 33409

At this site a total of 72 subjects were screened, 28 subjects enrolled in the study and 1 subject withdrew/discontinued. 27 subjects were randomized and completed the study. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study.

The medical records/source documents for 16 subjects' files were reviewed in depth including drug accountability records, inclusion/exclusion criteria, IRB records and compared source documents to data listings and primary efficacy endpoints and adverse events. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Scharf, Hull and Marcadis revealed no significant problems that would adversely impact data acceptability. The data submitted from the inspected sites are acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Antoine El-Hage
9/5/2008 01:27:02 PM
PHARMACOLOGIST

Constance Lewin
9/8/2008 09:46:29 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22036 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Silenor
Established Name: Doxepin HCl

Strengths: 1, 3 and 6 mg tablets

Applicant: Somaxon Pharmaceuticals, Inc.
Agent for Applicant (if applicable):

Date of Application: Jan 30, 2008
Date of Receipt: Jan 31, 2008
Date clock started after UN:
Date of Filing Meeting: Mar 5, 2008
Filing Date: March 16, 2008
Action Goal Date (optional):

User Fee Goal Date: Dec 1, 2008

Indication(s) requested: insomnia

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Spon has req small bus waiver; still under review
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, Years - **not given**

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 67,162

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) May 25, 2005 NO

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) June 28, 2006 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? Consult in progress YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? Consult in progress YES NO
- Risk Management Plan consulted to OSE/IO? YES NO
Consult in progress
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO

- | | | | | |
|---|-----|--------------------------|----|--------------------------|
| If EA submitted, consulted to EA officer, OPS? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| • Establishment Evaluation Request (EER) submitted to DMPQ? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| • If a parenteral product, consulted to Microbiology Team? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |

ATTACHMENT

MEMO OF FILING MEETING

DATE: [March 5, 2008](#)

NDA #: [22036](#)

DRUG NAMES: [Doxepin HCl](#)

APPLICANT: [Somaxon Pharma., Inc.](#)

BACKGROUND: 505 b2 application
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: see below

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	June Cai
Secondary Medical:	
Statistical:	Kun Jin, Tristan assie
Pharmacology:	Melissa Banks
Statistical Pharmacology:	
Chemistry:	Martha Heimann
Environmental Assessment (if needed):	
Biopharmaceutical:	Veneeta Tandon
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Constance Lewin
OPS:	Dan Brounstein
Regulatory Project Management:	Cathy Michaloski
Other Consults:	Stat for Carci;

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- | | | | | |
|---|--------------------|-------------------------------------|----|--------------------------|
| • Clinical site audit(s) needed?
If no, explain: | YES | <input checked="" type="checkbox"/> | NO | <input type="checkbox"/> |
| • Advisory Committee Meeting needed? | YES, date if known | _____ | NO | <input type="checkbox"/> |

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A X YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. Convey document filing issues/no filing issues to applicant by Day 74.

Cathleen Michaloski, BSN, MPH
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO
3 NDAs listed as reference drugs: Sinequan 16-798 (capsules), and Sinequan 17-516 (oral concentrate) and Zonalon 5% cream

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): [see above](#)
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”). **This application provides for a new indication (insomnia), new dosage formulation (tablets) and new strength (1, 3, 6 mg).**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? YES NO

(See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s): [None listed in Orange Book](#)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the

Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

See attached table NO

YES

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration



Data Ref 22036
ScanDoc.pdf (1...

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

/s/

Cathleen Michaloski
7/28/2008 11:39:27 AM
CSO

Cathleen Michaloski
7/28/2008 11:43:53 AM
CSO