CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-519

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
REPONSE TO AE LETTER

NDA:	21-519
Submission Code	BC-000
Submission Type	Response to AE letter: Labeling Changes
Submission Date(s):	June 20, 2007
Brand Name	Luvox®
Generic Name	Fluvoxamine Maleate
Formulation; Strength(s)	25mg , 50 mg, 100 mg immediate release oral tablet
Sponsor	Solvay Pharmaceutical
Primary Reviewer	Carol Noory
Team Leader	Raman Baweja
OCP Division	Division of Clinical Pharmacology I
ORM division	Division of Psychiatry Products (DPP) HFD-130
Indication	Obsessive Compulsive Disorder

I. TABLE OF CONTENTS

A. TABLE OF CONTENTS

II. EXECUTIVE SUMMARY

A. BACKGROUND

On November 16, 2006, an approvable letter was sent to Solvay Pharmaceuticals, Inc. regarding NDA 21519 along with labeling recommendations. The current submission of June 20, 2007 has the sponsor's labeling changes.

B. LABELING COMMENTS

The firm has included the Agency's recommended statements regarding the co-administration of fluvoxamine with ramelteon, tizanidine and alosetron.

1. The firm has added the following statements under ***DRUG INTERACTIONS; CNS Active Drugs:***
    a. ***Ramelteon:*** When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and fluvoxamine, the AUC for ramelteon increased approximately 190-fold and the C_{max} increased approximately 70-fold compared to ramelteon administered alone. Ramelteon should not be used in combination with fluvoxamine (see **WARNINGS**).
    b. ***Tizanidine:*** See **CONTRAINDICATIONS** and **WARNINGS.**

2. The firm has added the following statement under ***DRUG INTERACTIONS; Other Drugs:***
    a. ***Alosetron:*** Because alosetron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. Fluvoxamine is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 mg to 200 mg a day for 16 days, with co-administration of alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentration (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. (See **CONTRAINDICATIONS, PRECAUTIONS**, and Lotronex™ (alosetron) package insert.)

3. Under the **CONTRAINDICATIONS** section, the firm has added the following statement regarding tizanidine and alosetron.
    a. Co-administration of tizanidine, thioridazine, alosetron, or pimozide with LUVOX Tablets is contraindicated. (See **WARNINGS** and **PRECAUTIONS.**)

4. Under the **WARNINGS** section, the firm has added the following statements regarding the potential for interaction with tizanidine and alosetron.
    a. **Potential Tizanidine Interaction**
    Fluvoxamine is a potent inhibitor of CYP1A2 and tizanidine is a CYP1A2 substrate. The effect of fluvoxamine (100 mg daily for 4 days) on the pharmacokinetics and pharmacodynamics of a single 4 mg dose of tizanidine has been studied in 10 healthy male subjects. Tizanidine C_{max} was increased approximately 12-fold (range 5-fold to 32-fold), elimination half-life was increased by almost 3-fold, and AUC increased 33-fold (range 14-fold to 103-fold). The mean maximal effect on blood pressure was a 35 mm Hg decrease in systolic blood pressure, a 20 mm Hg decrease in diastolic blood pressure, and a 4 beat/min decrease in heart rate. Drowsiness was significantly increased and performance on the psychomotor task was significantly impaired. Fluvoxamine and tizanidine should not be used together. (See CONTRAINDICATIONS and PRECAUTIONS.)
    b. **Potential Alosetron Interaction**
    Fluvoxamine, an inhibitor of several CYP isozymes, has been shown to increase mean alosetron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. Consequently, it is recommended that fluvoxamine not be used in combination with alosetron (see CONTRAINDICATIONS, PRECAUTIONS, and Lotronex™ (alosetron) package insert).

5. In addition under "Information for Patients" the recommended statements regarding use of fluvoxamine with tizanidine and alosetron were added under the Concomitant Medication subsection.
    a. Because of the potential for the increased risk of serious adverse reactions including severe lowering of blood pressure and sedation when fluvoxamine and tizanidine are used together, fluvoxamine should not be used with tizanidine.
    b. Because of the potential for the increased risk of serious adverse reactions when fluvoxamine and alosetron are used together, fluvoxamine should not be used with Lotronex™ (alosetron).

6. The firm has made capitalization changes and provided numbered titles for the tables.

7. Under the **Drug Interactions,** ***Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes:*** the word "drug" appears twice in line 3. This should be corrected.

C. RECOMMENDATONS

The Office of Clinical Pharmacology has reviewed the pertinent parts of the "Clinical Pharmacology", "Drug Interactions" and the "Dosage and Administration" Sections of the labeling submitted in response to the approvable letter sent by FDA dated November 16, 2006. The labeling is acceptable as revised with a minor typographical correction (See "D" below)

D. LABELING COMMENTS TO BE SENT TO SPONSOR

Under the **Drug Interactions,** ***Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes:*** the word "drug" appears twice in line 3 as indicated below:

"Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also **WARNINGS** for details) and limited *in vitro* data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes that are known to be involved in the metabolism of other drugs ~~drugs~~ such as: CYP1A2 (e.g. warfarin, theophylline, propranolol, tizanidine), CYP2C9 (e.g. warfarin), CYP3A4 (e.g. alprazolam), and CYP2C19 (e.g. omeprazole)."

III. SIGNATURES

Reviewer:	Carol Noory	Date: _____
Team Leader:	Raman Baweja	Date: _____

cc list:
DFS: NDA 21-519 August 13, 2007

HFD-860: (NooryC, BawejaR, UppoorR, MehtaM)
HFD-120: (BenderW, LaughrenT, OliverT, DubitskyG, ClaffeyD)

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/s/

Carol Noory
8/13/2007 01:45:04 PM
BIOPHARMACEUTICS

Raman Baweja
8/13/2007 03:21:20 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Fluvoxamine
NDA: 21519
FORMULATION: Oral Tablet
APPLICANT: Solvay Pharmaceuticals

PRIMARY REVIEWER: Andre Jackson
TYPE: NDA
STRENGTH: 25 MG, 50 MG AND 100 MG
Submission Dates:
May 16, 2006
June 7, 2006

INDICATIONS: [redacted] b(4)

Background:

The firm has submitted a complete response to an approvable letter from the FDA dated February 9, 2004. This response contained only two items that required review by OCP. These items were the firm's response to the proposed OCP dissolution specification and a review of the firm's proposed label.

1.DISSOLUTION DATA:

FDA Comment:

Dissolution Method and Specification

We propose the following dissolution conditions for this application, which are the same as those for the original Luvox application. The conditions and specifications for all tablet strengths are:

Medium: 900 ml water at 37°C
Apparatus II: [redacted] at 50 rpm b(4)
Sampling Times: 10, 20 and 30 min
Q = [redacted] in 30 min

As part of your response to this letter, we ask that you confirm your acceptance of this method and specification.

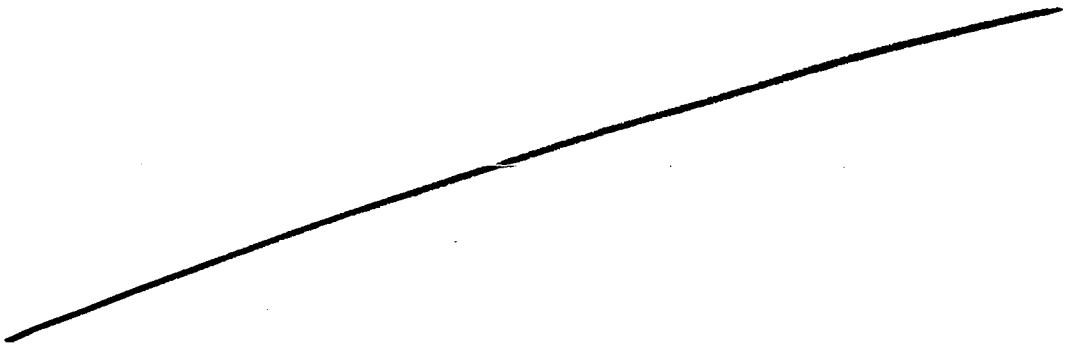
Firm's Response:

The firm has adopted the proposed dissolution methodology and specification proposed by the FDA, and the firm proposes to sample at only 30 min (Q=[redacted] in 30 min). This is acceptable to OCP. b(4)

Label:

2.FIRM'S PROPOSED LABEL(only the section that was changed by the firm is presented).

WARNINGS/Potential Interaction with Tizanidine



b(4)

Comment on Label :

1 The firm's proposed change to the label is acceptable to OCP. The section of the label presented contains some new information on a drug- drug interaction with Tizanidine. The firm supplied the following reference which was reviewed and summarized by OCP.

Summary of article by:
Granfors et al. Fluvoxamine drastically increases concentrations and effects of Tizanidine: A potentially hazardous interaction. Clin Pharmacol and Therap. 75 (4), 331-341, 2004.

A study was conducted in 10 healthy male adults ages 21-31. The study was done as a 2-phase crossover with a 4-week washout. Subjects were dosed with either 100 mg fluvoxamine or matched placebo once daily for 4 days. On day 4, 4 mg of tizanidine was administered in the am. A caffeine test was performed on the third day of pretreatment to evaluate association between CYP1A2 activity and tizanidine pharmacokinetics. Blood samples were taken at 20, 40, 60 and 90 minutes and 2, 3, 4, 5,7, 9, 12 and 24 hrs later. Blood pressure was determined before dosing and after each blood sample.

Results:

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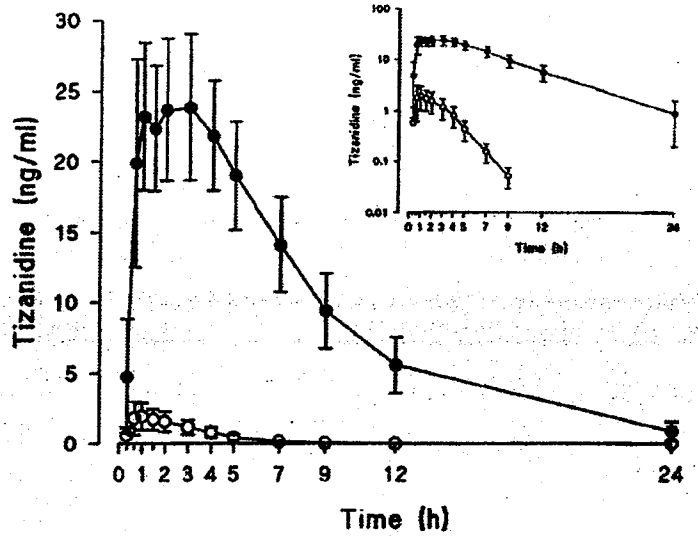

Fig 1. Mean ± SD plasma concentrations of tizanidine in 10 healthy volunteers after single oral dose of 4 mg tizanidine after treatment with placebo or 100 mg fluvoxamine once daily for 4 days. *Open circles*, Tizanidine during placebo; *solid circles*, tizanidine during fluvoxamine. *Inset* depicts the same data on a semilogarithmic scale. Time 0 refers to administration of tizanidine (ie, 1 hour after the last dose of fluvoxamine).

Best Possible Copy

Table II. Pharmacokinetic variables of 4 mg tizanidine in 10 healthy volunteers after 4-day pretreatment with 100 mg fluvoxamine or placebo

Variable	*Placebo phase (control)*	*Fluvoxamine phase*	*Difference between phases*	*P value*
C_{max} (ng/mL)	2.2 ± 0.9	26.6 ± 5.6	24.4 (19.9-28.8)	.000001
% of control and range	100	1210 (540-3210)		
t_{max} (min)	60 (40-120)	90 (40-240)		.17
$t_{1/2}$ (h)	1.5 ± 0.1	4.3 ± 1.1	2.8 (2.0-3.6)	.00004
% of control and range	100	290 (190-430)		
AUC(0-∞) (ng · h/mL)	6.6 ± 2.9	216.0 ± 51.6	209.3 (169.2-249.4)	.000002
% of control and range	100	3260 (1370-10350)		

Data are mean ± SD or mean with 95% CI; percentage of control is given with range; t_{max} data are given as median with range.
CI, Confidence interval; t_{max}, time to reach C_{max}; $t_{1/2}$, half-life; AUC(0-∞), area under plasma concentration-time curve from time 0 to infinity.

The mean results indicate a 12 fold increase in Cmax, 3 fold increase in half-life and a 33 fold increase in AUC for Tizanidine in the presence of fluvoxamine compared to placebo (tizanidine alone). There were significant drops in systolic and diastolic blood pressure in subjects receiving tizanidine concurrently with fluvoxamine versus the placebo group.

Comment on Article:

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1.This article supports the sponsor's new label statement.

Comments to the Clinical Division:

Fluvoxamine has a very pronounced effect on the pharmacokinetics of tizanidine. The Medical Officer should also check the statement related to blood pressure and heart rate in the label. This interaction is described in detail in the Warnings section. Additional cross references to the interaction are in the Contraindications and Precautions sections of the label. The mention of this drug interaction between tizanidine and fluvoxamine in the "Contraindications Section" is being deferred to the Medical team.

SIGNATURES

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-519, HFD-860(Mehta, Baweja, Jackson

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/s/

Andre Jackson
10/2/2006 09:57:21 AM
BIOPHARMACEUTICS

Raman Baweja
10/2/2006 12:14:14 PM
BIOPHARMACEUTICS

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10 COMPLETED NOV 2 5 2003

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Luvox ® (Fluvoxamine Maleate) **PRIMARY REVIEWER**: Andre Jackson
NDA:21-519
FORMULATION: Oral Tablet **STRENGTH: 25 mg, 50 mg, 100 mg**
APPLICANT: Solvay Pharmaceuticals Submission Date: June 28, 2002
INDICATIONS: Obsessive Compulsive Disorder **September 5, 2003**
Generic Name: Fluvoxamine Maleate

History

LUVOX® (fluvoxamine maleate) 25 mg, 50 mg, and 100 mg Tablets were originally approved as NDA 20-243 on 05 December 1994 for the indication of Obsessive Compulsive Disorder for use in adults and for use in children and adolescents since 25 March 1997.

In September 1997, Solvay Pharmaceuticals, Inc., the owner/applicant for the product, was placed under the Application Integrity Policy (AIP). As a result of the AIP, a thorough audit and validity assessment of the LUVOX® Tablets application was conducted. The AIP audit revealed instances where inaccurate or unsubstantiated chemistry, manufacturing and controls data had been submitted to the Food and Drug Administration, As a result of this audit and as part of an agreement between the Agency and Solvay Pharmaceuticals, Inc., NDA 20-243 was withdrawn in a letter dated 13 May 2002.

Introduction Current Submission

Solvay Pharmaceuticals is requesting that all nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability and clinical safety and efficacy information contained in NDA 20-243, including supplements S-006 and S-021 , be included by reference in this New Drug Application (NDA 21-519) for LUVOX® Tablet. A new NDA number 21519 was assigned to Luvox because the earlier NDA for Luvox 20,243 had been withdrawn. The clinical indication is the same (i.e., obsessive compulsive disorder for use in adults and for use in children and adolescents).

The firm is requesting re-instatement of the data (i.e., to be used in NDA 21-519) for the 100 mg, 50 mg and 25 mg fluvoxamine maleate tablet bioequivalence studies from NDA 20-243 since the audit of the bioanalytical data associated with the pharmacokinetics and bioavailability data did not identify any issues that would invalidate the data.

The bioequivalence of LUVOX® Tablets to the clinical materials used in pivotal efficacy and safety trials was demonstrated by data previously submitted to the Agency in NDA 20-243.

The firm conducted the following bioequivalence studies linking their capsule formulations which were used in clinical trials to the to-be-marketed tablet formulations. The studies were:

1. **Protocol H.114.6007-BIOAVAILBILITY OF FLUVOXAMINE, enteric coated tablets, breakable film-coated tablets, capsules and solution.-** DONE IN 1993

2 x 50 mg Fluvoxamine film coated tablets, 2x50 mg new breakable Fluvoxamine film coated tablet, 2x50 mg Fluvoxamine maleate enteric coated tablets, and either 2x50 mg Fluvoxamine maleate in a hard gelatin capsule or [redacted] b(4)

Parameter	Film coated vs capsule
AUC0-T	88-103
Cmax	87-107

2.Protocol RH.114.00.03-(Report No. CR100.007)-Full Scale study-DONE IN 1991

50 mg Fluvoxamine film coated tablet (**to be marketed in US**) vs 50 mg Gray opaque capsules(**used in US studies for OCD**.) Study CI reported in V1.14 page 3720 were:

Parameter	
AUC0-T	97-103
AUC0-inf	98-102
Cmax	94-106

3.Protocol RH.114.02.03-(Report No. CR100.0032)--Full Scale study-Done in 1992

50 mg Fluvoxamine Maleate film-coated tablet (**to be marketed in US**) vs 2 x 25 mg and 50 mg Opaque CAPSULES(**used in US studies for OCD**). Study CI reported in V1.14 page 3840 were

Parameter	50 mg tablet vs 2X 25 mg capsules	50 mg tablet vs 50 mg capsules
AUC0-T	95-109	99-113
AUC0-inf	96-107	99-111
Cmax	91-105	97-112

A formal bioequivalence study was not done on the 25 mg tablet, however it is compositionally proportional to the 50 mg and 100 mg tablets for which bioequivalence studies were conducted.

Addendum to Review:

The firm was requested to provide information related to the sameness of the formulations, manufacturing procedures and dissolution methodology between the current NDA 21-519 and the approved NDA 20-243 which had been previously withdrawn.

OCPB Question 1.

Qualitatively and quantitatively are the formulations for the 25 mg, 50 mg and 100 mg tablets in the current NDA 21-519 are identical to the formulations approved under NDA 20-243?

Firm's Response

Solvay confirms that qualitatively and quantitatively the formulations for the 25 mg, 50 mg and the 100 mg filed in the current NDA, 21-519, are identical to that approved in NDA 20-243. The formulations for the 25 mg, 50 mg and 100 mg tablets submitted in NDA 20-243 and in NDA 21-519 are provided in Attachment 1 and Attachment 2, respectively.

OCPB Question 2.

Are the manufacturing procedures and site location for the manufacture of the 25 mg, 50 mg and 100 mg tablets in the current NDA 21-519 identical to the manufacturing procedures and site location for the formulations approved under NDA 20-243?

Firm's Response

Solvay confirms that the manufacturing procedures and the site location for the manufacture of the 25 mg, 50 mg and 100 mg tablets in the current NDA 21-519 are identical to the manufacturing procedures and site location for the formulations approved under NDA 20-243. The manufacturing procedures and site location submitted in NDA 20-243 and in NDA 21-519 are provided in Attachment 3 and Attachment 4, respectively.

OCPB Question 3.

Are the dissolution method and specification for the 25 mg, 50 mg and 100 mg tablets in current NDA 21-519 identical to those in approved NDA 20-243 and will these be maintained for the current NDA 21-519?

Frim's Response

Solvay confirms that the dissolution method and specification for the 25 mg, 50 mg

and 100 mg tablets in current NDA 21-519 are and will be identical to those in the approved NDA 20-243. The dissolution method and specifications for the 25 mg, 50 mg and 100 mg tablets submitted and approved in NDA 20-243 (from the amendment of 9 September 1994 response to approvable letter) and submitted in . NDA 21-519 are provided in Attachment 5 and Attachment 6, respectively.

Comments:

1. The composition for the 25 mg, 50 mg and 100 mg Luvox tablets in the new NDA 21-519 are the same as for NDA 20-243 for which the bioequivalence studies were conducted. The formulas are given in Tables 1.1-1.3.

1.1 Composition of Fluvoxamine Maleate 25 mg Tablets

COMPONENT	mg/tablet
[redacted]	
Fluvoxamine Maleate	25.0
Mannitol USP	
Pregelatinized Starch NF (Potato)	
Starch NF (Corn)	
[redacted]	
Silicon Dioxide NF	
Sodium Stearyl Fumarate NF	
TOTAL	
[redacted]	
[redacted]	
[redacted]	
Carnauba Wax NF	
TOTAL	129

b(4)

* Component quantities with the exception of the drug substance may vary within the range of [redacted] to allow for a small amount of normal operational variation. It is not our intent to arbitrarily vary the quantity of the inert ingredients from the stated formula. However, normal operational variations occasionally result in problems which can be alleviated, by minor adjustments in the formula. This proposed range will allow for such adjustments in a timely manner.

** Due to the inherent variances associated with the film coating process the above quantities are theoretical amounts which approximate the quantitative composition.

1.2 Composition of Fluvoxamine Maleate 50 mg Tablets

COMPONENT	mg/tablet
[redacted]	
Fluvoxamine Maleate	50.0
Mannitol USP	
Pregelatinized Starch NF (Potato)	
Starch NF (Corn)	
[redacted]	
Silicon Dioxide NF	
Sodium Stearyl Fumarate NF	
TOTAL	
[redacted]	
[redacted]	
[redacted]	
Carnauba Wax NF	
TOTAL	258

b(4)

* Component quantities with the exception of the drug substance may vary within the range of [redacted] to allow for a small amount of normal operational variation. It is not our intent to arbitrarily vary the quantity of the inert ingredients from the stated formula. However, normal operational variations occasionally result in problems which can be alleviated, by minor adjustments in the formula. This proposed range will allow for such adjustments in a timely manner.

** Due to the inherent variances associated with the film coating process the above quantities are theoretical amounts which approximate the quantitative composition.

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1.3 Composition of Fluvoxamine Maleate 100 mg Tablets

COMPONENT	mg/tablet
[redacted]	
Fluvoxamine Maleate	100.0
Mannitol USP	
Pregelatinized Starch NF (Potato)	
Starch NF (Corn)	
[redacted]	
Silicon Dioxide NF	
Sodium Stearyl Fumarate NF	
TOTAL	
[redacted]	
[redacted]	
[redacted]	
Carnauba Wax NF	
TOTAL	516

b(4)

* Component quantities with the exception of the drug substance may vary within the range of [redacted] to allow for a small amount of normal operational variation. It is not our intent to arbitrarily vary the quantity of the inert ingredients from the stated formula. However, normal operational variations occasionally result in problems which can be alleviated, by minor adjustments in the formula. This proposed range will allow for such adjustments in a timely manner.

** Due to the inherent variances associated with the film coating process the above quantities are theoretical amounts which approximate the quantitative composition.

2.The dissolution conditions for the new NDA 21-519 are the same as for NDA 20-243 for which the bioequivalence studies were conducted. The conditions and specifications are:

Medium	900 ml water at 37 ^{0}C
ApparatusII	[redacted] at 50 rpm
Sampling Times:	10, 20 and 30 min
Q	NLT [redacted] in 30 min

3.OCPB has no Clinical Pharmacology issues related to the approval of this NDA 21-519

Andre Jackson

RD/FT Initialed by Raman Baweja, Ph.D. R. Baweja 11/24/03

Cc-NDA 21-519, HFD-860(Jackson, Baweja,Sahajwalla, Mehta), Central Documents Room(Biopharm-CDR)

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/s/

Andre Jackson
11/24/03 01:58:31 PM
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Raman Baweja
11/24/03 02:49:20 PM
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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21519**	**Brand Name**	**Luvox®**
OCPB Division (I, II, III)	**DPE I**	**Generic Name**	**Fluvoxamine**
Medical Division	**Neuropharmacology, HFD-120**	**Drug Class**	**Serotonin reuptake inhibitor**
OCPB Reviewer	**Andre Jackson**	**Indication(s)**	**Obsessive Compulsive Disorder(OCD)**
OCPB Team Leader	**Ray Baweja**	**Dosage Form**	**Tablet**
		Dosing Regimen	**BID**
Date of Submission	**To be determined**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**To be determined**	**Sponsor**	**Solvay**
PDUFA Due Date	**To be determined**	**Priority Classification**	**1 S**
Division Due Date	**To be determined**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]	[redacted]	
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]

solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	X	4(RH114.00.02 -Pilot study ;RH.114.00.03 50 mg study; RH114.02.03 50 mg study;S114.1.1 05)		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waivier	X			
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	5		

Background:

The firm is currently under Application Integrity Policy due to inaccurate or unsubstantiated chemistry, manufacturing and controls data having been submitted to the FDA. The current submission contains the following studies:

1).Protocol # H 114.6007-STUDY CONDUCTED IN 1992
2 x 50 mg -film coated tablet-new breakable tablet
2 x 50 mg enteric coated tablets-marketed in Europe
2 x 50 mg hard gelatin capsule-used in clin trials

b(4)

2).Protocol RH.114.00.02-Pilot Study
50 mg Fluvoxamine film coated tablet vs Gray opaque capsules.

3).Protocol RH.114.00.03-Full Scale study- Study was done in 1991.
50 mg Fluvoxamine film coated tablet (to be marketed in US) vs 50 mg Gray opaque capsules(used in US studies for OCD)

4).Protocol RH.114.02.03-Full Scale study-Study was done in 1992.
50 mg Fluvoxamine Maleate film-coated tablet (to be marketed in US) vs 2 x 25 mg and 50 mg Opaque capsules(used in US studies for OCD).

5).Protocol S114.1.105- Study was done in 1999.
US film coated 100 mg tablet Luvox vs European 100 mg tablet Fevarin
To demonstrate the in-vivo BE of US and European fluvoxamine tablets.

During the filing meeting the possible comparability (i.e., similarity or sameness) of the current 50 mg tablets to those used in the original NDA was discussed. It was noted that if the formulations were similar (e.g., Supac IR level 1), then the firm would only need to apply for a waiver for the 50 mg Fluvoxamine film coated tablet. If the 50 mg tablet formulations are identical then a waiver is not required. Resolution of this point would require the firm supplying qualitative and quantitative formulations and dissolution data for the original and current 50 mg film coated tablets.

Filability and QBR comments		
	"X" if yes	Comments
Application fileable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		1.What are the formulations (qualitative and quantitative) for the proposed 50 mg film coated tablet (NDA 21519) and the original 50 mg film coated tablet submitted in NDA 20-243. 2.You should supply dissolution data comparing the original and current fomulations using the original NDA dissolution conditions and specifications. 3.You should submit a formal waiver request and formulations for all strengths you wish to market. 4.Include complete assay validation data for each study especially assay dates, sample storage times, long term plasma stability, freeze-thaw, bench top stability and assay recovery.
QBR questions (key issues to be considered)	**Please refer to background and comments section above.**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Andre Jackson**	
Secondary reviewer Signature and Date		

CC: NDA 21519 HFD-850 (Lee), HFD-120 (Ware,CSO), HFD-860 (Jackson, Baweja, Mehta), CDR (Biopharm-CDR)

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