CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-519

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #21-519

Sponsor:	Solvay Pharmaceuticals
Drug:	Luvox (fluvoxamine maleate)
Proposed Indication:	OCD (adults & pediatric patients)
Material Submitted:	Response to 11-16-06 AE Letter
Date Submitted:	June 20, 2007
Date Received:	June 21, 2007

I. Regulatory History

Luvox (fluvoxamine maleate) is a selective serotonin reuptake inhibitor (SSRI) that was approved by the Agency for use in the treatment of obsessive-compulsive disorder (OCD) on 12-5-94 under NDA 20-243.

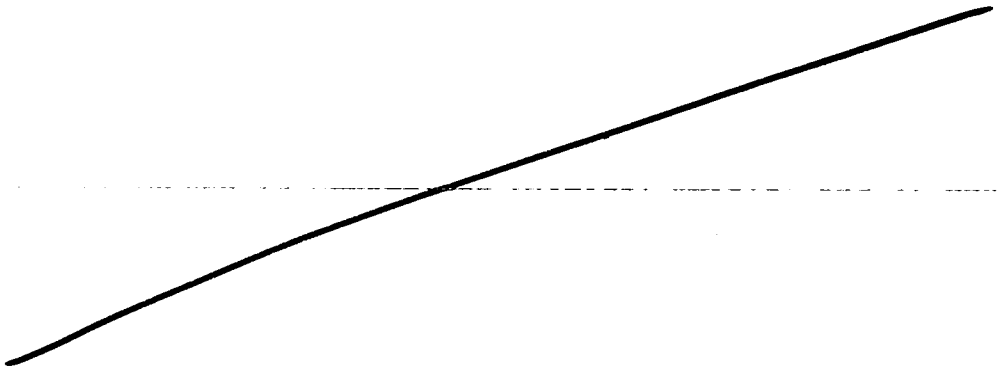
The sponsor, Solvay Pharmaceuticals, was placed under the Application Integrity Policy (AIP) by the CDER Center Director on 9-24-97 for a number of reasons, including the submission of falsified data to the Agency. As part of the consent agreement to be removed from AIP, Solvay withdrew NDA 20-243 on 5-14-02. Solvay then submitted the current NDA, which comprised Chemistry, Manufacturing and Controls (CMC) and biopharmaceutics data, with all clinical safety and efficacy data incorporated by reference to the withdrawn NDA.

On 4-9-03, Solvay was removed from AIP and the review clock for this application started on that date. Reviews of that submission were completed and an APPROVABLE (AE) letter was issued on 2-9-04. This letter delineated a number of requests pertaining to CMC and Pharmacology/Toxicology issues, proposed dissolution method and specification conditions, revised labeling, a post-marketing commitment to perform juvenile animal studies, and promotional materials.

A response to that AE letter was submitted on 5-16-06 and was examined by the FDA review teams. Following completion of these reviews, the application was again deemed to be approvable, with final approval contingent on responses to

has been superseded by a revised Medication Guide for all antidepressants (see below).

There are a number of other changes initiated by the sponsor in their 6-20-07 proposed labeling. Most of these are minor editorial changes such as revision of table numbering, utilizing a subscript font for C_{max} and C_{min}, correction of a few typographical errors, placing adverse events in alphabetical order in a few event listings, and adding the word "See" in cross-references. These are all deemed to be acceptable by the undersigned reviewer. More substantive changes are:



b(4)

• under PRECAUTIONS-Drug Interactions-Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes, summarization in text form of cytochrome P450 isozymes (and examples of drugs metabolized by the isozymes) which are likely inhibited by fluvoxamine. This information was previously presented in a tabular format. Although a table is preferable to text in my opinion, I have no strong objection to this change.
• under ADVERSE REACTIONS-Postmarketing Reports, the event "amenorrhea" was added to the adverse event listing. No explanation for this change was provided. A survey of the FDA AERS DataMart on 7-5-07 revealed a total of ten reports of amenorrhea with Luvox listed as the suspected drug. Thus, I have no strong objection to adding this event to this section.

On 8-1-07, sponsors of antidepressant drugs were requested to modify certain sections of labeling pertaining to treatment-emergent suicidality. These changes are pursuant to an FDA-completed analysis of suicidality in clinical trials in adults treated with antidepressant agents, a meeting of the Psychopharmacologic Drugs Advisory Committee on 12-13-06, and comments from sponsors regarding FDA-

outstanding pharmacology/toxicology and CMC issues and revision of labeling to incorporate recent changes to the labeling which had been implemented for the Reference-Listed-Drug (RLD).[1] A delineation of the issues to be addressed by Solvay prior to approval were communicated to the sponsor in a second AE letter dated 11-16-06.

This submission contains Solvay's response to the second AE letter and includes revised proposed labeling.

In addition, this submission contains the final report for Study 114.2.09 entitled "Fluvoxamine: A Multicenter, Placebo-Controlled, Randomized, Double-Blind, Relapse Prevention Study in the Maintenance Treatment of Outpatients with Obsessive Compulsive Disorder." This study, which was conducted between January 1996 and November 2000, was performed to satisfy a Post-Marketing Commitment at the time of approval of the original NDA in 1994 to conduct an adequate and well-controlled relapse prevention study in patients with OCD.

The submission of this study report and the [redacted] to this application are not permitted at this time, according to the current Prescription Drug User Fee Act (PDUFA). The Project Manager and Chief Project Manager, William Bender and Paul David, respectively, consulted with User Fee staff at the FDA as well as with Solvay. It was agreed that this study report and the corresponding [redacted]

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The sole clinical issue for review at this time is the sponsor's proposed labeling. The findings from the labeling review are summarized below.

II. Clinical Review of Proposed Labeling

The "Labeling" section of the 11-16-06 AE letter contained 22 items regarding FDA-requested revisions to the product labeling to be addressed by the sponsor. Solvay's proposed labeling, submitted on 6-20-07, was examined by the undersigned reviewer with respect to each of those items. Each item appears to be satisfactorily addressed except for the last item (#22), which is no longer applicable since it

[1] Sandoz fluvoxamine maleate tablets.

proposed language for these sections which we requested on 5-1-07.

In their 8-8-07 revised labeling, Solvay had incorporated the changes requested on 5-1-07 but two additional minor changes are required based on our 8-1-07 letter (see Conclusions and Recommendations below). Otherwise, the sponsor's language for these sections in their 8-8-07 proposal is acceptable.

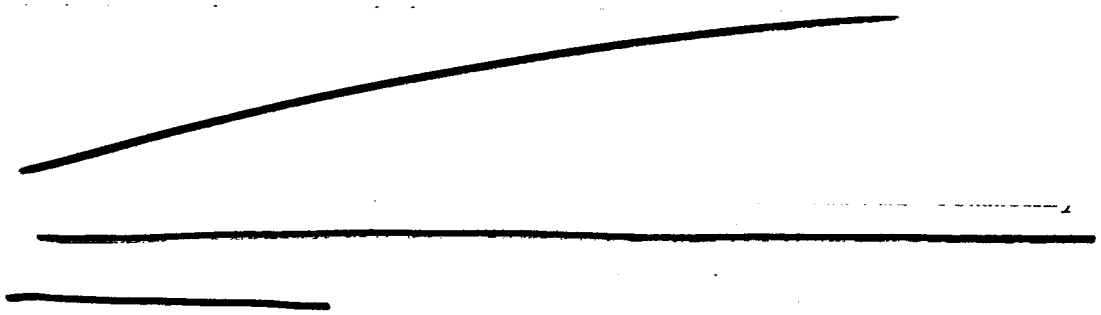
In addition, a letter to sponsors of SSRI antidepressants was issued on 8-7-07 requesting revisions to the following sections of labeling regarding hyponatremia associated with these agents:

- PRECAUTIONS, General.
- PRECAUTIONS, Geriatric Use.

These revisions must also be implemented in the sponsor's proposed labeling.

III. Conclusions and Recommendations

The sponsor's 6-20-07 labeling should be revised as follows:



b(4)

2) changes to the following sections, which pertain to suicidality and antidepressant drugs, should be revised in accordance with our 8-1-07 letter to antidepressant sponsors:

- Boxed Warning-Suicidality and Antidepressant Drugs,
- WARNINGS-Clinical Worsening and Suicide Risk,

[2] It is noted that these data were removed in the sponsor's 8-8-07 labeling.

• PRECAUTIONS-Information for Patients-Clinical Worsening and Suicide Risk, and
• Medication Guide.

These sections, as presented in the 8-8-07 version of the sponsor's labeling, are acceptable if the following two changes are made:

• under WARNINGS, Table 5, the subheadings in the right-hand column should read "Increases Compared to Placebo" and "Decreases Compared to Placebo" instead of [redacted] respectively.
• in the Medication Guide, the sentence designated as #1 should end with the phrase "within the first few months of treatment" instead of [redacted] b(4)

3) information related to SSRI-associated hyponatremia must be added to the following sections, in accordance with our 8-7-07 letter to antidepressant sponsors:

• PRECAUTIONS, General.
• PRECAUTIONS, Geriatric Use.

Once agreement has been reached on these labeling changes and all Pharmacology-Toxicology and CMC concerns have been adequately addressed, it is recommended that this NDA be approved.

Gregory M. Dubitsky, M.D.
August 27, 2007

cc: NDA #21-519
HFD-130 (Division File)
HFD-130/Dubitsky
/Cai
/Khin
/Mathis
/Laughren
/Bender

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/s/

Greg Dubitsky
8/27/2007 02:52:10 PM
MEDICAL OFFICER

Ni Aye Khin
8/31/2007 03:48:23 PM
MEDICAL OFFICER
I concur with Dr. Dubitksky's recommendations.

Review and Evaluation of Clinical Data
NDA #21-519

Sponsor:	Solvay Pharmaceuticals
Drug:	Luvox (fluvoxamine maleate)
Proposed Indication:	OCD
Date Submitted:	May 16, 2006
Date Received:	May 17, 2006
PDUFA Due Date:	November 17, 2006

I. Background

Luvox (fluvoxamine maleate) is a selective serotonin reuptake inhibitor (SSRI) that was approved by the Agency for use in the treatment of obsessive-compulsive disorder (OCD) on 12-5-94 under NDA 20-243.

The sponsor, Solvay Pharmaceuticals, was placed under the Application Integrity Policy (AIP) by the CDER Center Director on 9-24-97 for the following reasons: falsified stability data, falsified and missing data for drug interaction studies after approval, and other Chemistry, Manufacturing, and Controls (CMC) information that was deemed to be falsified or missing.

As part of the consent agreement to be removed from AIP, Solvay withdrew NDA 20-243 on 5-14-02. Solvay then submitted the current NDA, which comprised CMC and biopharmaceutics data, with all safety and efficacy data incorporated by reference to the withdrawn NDA.

On 4-9-03, Solvay was removed from AIP and the review clock for this application started on that date. Reviews of the original submission were completed and an APPROVABLE (AE) letter was issued on 2-9-04. This letter delineated a number of requests pertaining to CMC and Pharmacology/ Toxicology issues, proposed dissolution method and specification conditions, revised labeling, a post-marketing commitment to perform juvenile animal studies, and promotional materials.

This review will focus on the clinical sections of the revised labeling provided by the sponsor.

II. Clinical Review

A number of minor editorial changes have been made by the sponsor throughout labeling (e.g., removal of the "®" symbol following LUVOX). Unless noted below, these changes are judged to be acceptable.

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[1] Granfors MT, et al. Fluvoxamine drastically increases concentrations and effects of tizanidine: A potentially hazardous interaction. Clin Pharmacol Ther 2004;75:331-341.

10 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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III. Conclusions and Recommendations

From a clinical perspective, final approval is recommended after negotiation and mutual agreement between the sponsor and the Agency on the above points in product labeling.

Gregory M. Dubitsky, M.D.
September 29, 2006

cc: NDA #21-519
HFD-130 (Division File)
HFD-130/GDubitsky
/JCai
/NKhin
/MMathis
/TLaughren
/RGrewal
/WBender

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/s/

Greg Dubitsky
9/29/2006 02:05:30 PM
MEDICAL OFFICER

Ni Aye Khin
10/3/2006 09:09:51 AM
MEDICAL OFFICER
I concur with Dr. Dubitsky's recommendations.

MEMORANDUM

DATE: February 8, 2004

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-519

SUBJECT: Action Memo for NDA 21-519, for the use of Luvox (fluvoxamine maleate) Tablets in the treatment of Obsessive Compulsive Disorder (OCD)

NDA 21-519, for the use of Luvox (fluvoxamine maleate) Tablets in the treatment of Obsessive Compulsive Disorder (OCD), was submitted by Solvay Pharmaceuticals on 6/28/02. Luvox had previously been approved for the treatment of OCD on 12/5/94; however, Solvay Pharmaceuticals had been placed under the Application Integrity Policy (AIP) on 9/24/97 because of the submission of falsified data, and, as part of the consent agreement that would permit the sponsor to be removed from the AIP, the original NDA was withdrawn on 5/14/02. Solvay was removed from the AIP on 4/9/03, which permitted the current NDA to be reviewed, resulting in the current PDUFA due date of 2/9/04. The application contains CMC data and results of Segment I and Segment II reproductive toxicology studies in the rat submitted in fulfillment of a Phase 4 commitment imposed at the time of the original approval on 12/5/94. The sponsor requested that the Agency rely on all other previously submitted data for this application, given the company's assertion that the product proposed in this current application is identical to that approved in 1994, and that no data other than CMC data had previously been falsified or were the basis for their placement under the AIP.

The application has been reviewed by Dr. Greg Dubitsky, medical officer (review dated 1/5/04), Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/24/03), Dr. Linda Fossom, pharmacologist (review dated 2/9/04), Dr. Lois Freed, pharmacology Team Leader (memo dated 2/9/04), Dr. Lorenzo Rocca, chemist (review dated 1/29/04), and Dr. Tom Laughren, psychiatric drugs Team Leader (memo dated 2/4/04). The review team recommends that the application be considered Approvable (in particular, the Office of Compliance has recommended approval of the application on 8/11/03). I have only a few comments.

While in general the review team has concluded that the sponsor may rely on previously submitted data to support the approval of this application, there are still several outstanding deficiencies that the sponsor must address before the application may be approved.

Dr. Rocca has identified a number of issues that must be addressed.

Further, Dr. Fossom has reviewed the Segment I and II studies and finds them acceptable. However, she has identified another issue that the sponsor has not resolved.

There are 5 impurities in the drug substance for which the proposed specifications are above the level of qualification (0.15%), and [redacted] impurities/degradants in the drug product for which the proposed specifications are above the level of qualifications. These impurities and their proposed specifications are given below: b(4)

	Drug Substance	Drug Product
[redacted]		

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All of the proposed specifications for the impurities in the drug substance are below the specifications of the previously approved product, but two of the specifications for the impurities in the drug product are greater than the specifications in the previously approved product.

Typically, to qualify impurities present in these amounts, the sponsor would need to perform a general toxicology study of 2 weeks-3 months in one species, genotoxicity studies, a Segment II study, and a juvenile animal study (Luvox is "approved" for patients 8 years old and older).

As Dr. Fossom describes, the sponsor has performed a 13 week rat toxicology study with drug with [redacted], so this impurity has been qualified (at least regarding general toxicology). In addition, an examination of the product used in the recently submitted Segment II study shows that all impurities save for the [redacted] and the [redacted] have been qualified in this assay. None of the impurities have been subject to genotoxicity tests, and no juvenile animal studies have been done (juvenile animal studies will need to be performed in two species for an assessment of the general toxicology, but the impurities need be qualified in only one species). b(4)

The sponsor asserts that it is likely that all of the impurities were in drug substance lots used in the previously performed and submitted toxicology studies, based on specifications for these impurities in these lots. However, specific amounts actually present in those lots were not submitted.

Further, the sponsor notes that the specifications for the [redacted] and [redacted] were higher than those proposed here for various older formulations approved in over 40 countries between 1983-1997, and that the product was approved in 1993 in Canada, Sweden, the UK, and the Netherlands with higher specifications than those proposed here. Again, they have not submitted the levels of these impurities actually present in the product approved in these countries. b(4)

Dr. Fossom concludes that the [redacted] has been qualified for general toxicology, and that the [redacted] need not be further qualified for reproductive toxicology or general toxicology (because the specification for these latter is only slightly greater than the level of qualification). However, as Dr. Freed notes, the sponsor has synthesized the latter impurities, and, since the specifications for these impurities are greater than the limit of qualification, and additional qualifying toxicology studies for other impurities must be performed in any event, it seems reasonable for the sponsor to include these latter compounds in these necessary qualification studies. b(4)

In summary, then, all impurities must be assayed for genotoxicity and assessed in a juvenile animal toxicology study (this latter may be performed in Phase 4), if they are not lowered to below the level of qualification. In addition, as noted above, all of the impurities except the [redacted] must be qualified in a general toxicology study, and the [redacted] and the [redacted] must be qualified in a Segment II study. Of course, we would have no objection to the sponsor including all impurities/degradants in all qualifying studies. As noted, while the sponsor has proposed that previous human experience supports the qualification of the [redacted] Dr. Fossom notes that actual levels of this impurity to which patients have been exposed have not been submitted. The sponsor must also perform juvenile animal toxicology studies in two species (rodent and non-rodent) in Phase 4; one of the studies should qualify the impurities/degradants. b(4)

Finally, Dr. Dubitsky notes in his review that one of the reasons that the sponsor was placed under the AIP was due to missing/falsified data for drug interaction studies submitted after the original approval. While this will not affect the current action, we will need to obtain details about this issue before approval of the application. If these data are described in current labeling, and they are unreliable, additional changes to labeling may be required.

For the reasons given, then, I will issue the attached Approvable letter, with appended draft labeling.

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/s/

Russell Katz
2/9/04 12:21:00 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #21-519

Sponsor:	Solvay Pharmaceuticals
Drug:	Luvox (fluvoxamine maleate)
Proposed Indication:	OCD
Date Submitted:	June 28, 2002
Date Received:	July 1, 2002
PDUFA Due Date:	February 9, 2004

I. Background

Luvox (fluvoxamine maleate) is a selective serotonin reuptake inhibitor (SSRI) that was approved by the Agency for use in the treatment of obsessive-compulsive disorder (OCD) on 12-5-94 under NDA 20-243.

The sponsor, Solvay Pharmaceuticals, was placed under the Application Integrity Policy (AIP) by the CDER Center Director on 9-24-97 for the following reasons: falsified stability data, falsified and missing data for drug interaction studies after approval, and other Chemistry, Manufacturing, and Controls (CMC) issues that were deemed to be falsified or missing.

As part of the consent agreement to be removed from AIP, Solvay withdrew NDA 20-243 on 5-14-02. Solvay then submitted the current NDA, which comprises CMC and biopharmaceutics data, with all safety and efficacy data incorporated by reference to the withdrawn NDA.

On 4-9-03, Solvay was removed from AIP and the review clock for this application started on that date.

The clinical review of this application focuses on the following issues:

1) safety information from 2 newly submitted bioequivalence studies.
2) financial disclosure information.
3) request for a waiver of the requirement for pediatric studies in OCD.
4) recently recommended changes to the labeling of fluvoxamine generic products and other SSRI's.

II. Clinical Review

A. Safety Data from Bioequivalence Studies

Two new bioequivalence studies are reported in this application. Safety results from these investigations were examined by the undersigned to detect any serious adverse experiences associated with the administration of fluvoxamine which have not been previously noted.

1. Study H.114.6007

This was an open-label, randomized, cross-over study in 42 healthy male volunteers. Subjects received a single dose of 100mg of fluvoxamine as film-coated tablets, enteric-coated tablets, and capsules or oral solution to determine bioequivalence of these formulations.

No serious adverse experiences were reported. The most common treatment-emergent signs and symptoms were nausea and vomiting, headache, and diarrhea.

2. Study S114.1.105

This was an open-label, randomized, cross-over study in 29 healthy male subjects who received a single dose of fluvoxamine 100mg as the European-marketed tablet (Fevarin) and the U.S.-marketed film-coated tablet (Luvox).

There were no serious events reported. The most commonly reported adverse events with the U.S. product were tiredness, diarrhea, and nausea and, with the European formulation, diarrhea, nausea, and dizziness. All events resolved without sequelae.

B. Financial Disclosure Information

This application was amended on 8-12-02 to provide, among other items, financial disclosure information. Only study S114.1.105 is considered a "covered study" as defined in 21 CFR 54.2(e).[1]

For one of the two clinical investigators in this study [redacted], it was certified that: 1) Solvay had not b(4)

[1] Study H114.6007 was completed in 1992 and, thus, is not subject to financial disclosure requirements.

entered into any financial arrangement whereby investigator compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), 2) this investigator had no proprietary interest in this product or a significant equity interest in the sponsor as defined in 21 CFR 54.2(b), and 3) this investigator was not the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

For the other investigator [redacted] a financial disclosure statement could not be obtained despite due diligence since the investigator no longer works at the site. b(4)

C. Request for Pediatric Waiver

In their 8-12-02 amendment to this application, the sponsor requested a full waiver of pediatric studies in newborns, infants, children ages 2-11, and adolescents ages 12-16. Solvay has already completed a study of the safety and efficacy of Luvox in pediatric patients (ages 8-17) with OCD (study 114.02.01), a multiple-dose pharmacokinetic study in patients ages 6-17 (study S1141102), and a study of longer-term safety in patients ages 8-17 (study 114.02.01(E)).

We have viewed age 7 as the lower age limit for OCD Pediatric Written Requests. In my opinion, it is reasonable to waive the need to study pediatric patients age 7 as a separate group and I recommend granting the waiver as requested.

D. Revisions to Labeling of Generic Fluvoxamine Products and Other SSRI's

Solvay submitted [redacted] on 5-8-02 [redacted] that provided for the addition of a statement under WARNINGS regarding reports of NMS-like symptoms when fluvoxamine is co-administered with antipsychotics. This [redacted] was examined by the undersigned and findings were summarized in a 5-8-03 E-Mail to Thomas Laughren, M.D., Team Leader of the Psychiatric Drug Products Group. Subsequently, labeling language regarding this issue was formulated and communicated to the Office of Generic Drugs (OGD) since, at that time, Luvox b(4)

was not marketed and a generic fluvoxamine product was the reference listed drug.[2]

This same communication conveyed language to be added to the PRECAUTIONS section of generic fluvoxamine products regarding the risk of bleeding-related adverse events (BRAE's) associated with SSRI treatment based primarily on published studies. These studies and information from NDA databases are summarized and critiqued in a review completed on 11/19/03 by Alice Hughes, M.D., of the Division Safety Team. This review serves as the basis for a class labeling action underway at this time for all SSRI's.

In addition, we are in the process of requesting class labeling changes to provide information on symptoms which emerge upon discontinuation of SSRI's and serotonin norepinephrine reuptake inhibitors (SNRI's) as well as the effects of SSRI and SNRI exposure during the third trimester of pregnancy in neonates. This information will be added under PRECAUTIONS and DOSAGE AND ADMINISTRATION and is based on reviews of spontaneously reported events in the Agency's postmarketing safety database (AERS) as well as reports from the published literature. This information is summarized in 11-27-01 and 12-21-01 reviews completed by the Office of Drug Safety and in a clinical review dated 5-6-02 by Robert Levin, M.D., of the Psychiatric Drug Products Group.

These revisions, as currently requested, are presented in the Appendix to this review.

III. Conclusions and Recommendations

Examination of the safety data from the two additional bioequivalence studies revealed no serious adverse events associated with single dose fluvoxamine administration.

Financial disclosure information is adequate.

I recommend granting a full waiver for further pediatric studies in OCD, as requested by the sponsor.

As mentioned above, Luvox labeling should incorporate revisions pursuant to SLR-014 for NDA 20-243 as well as

[2] See a 5-14-03 E-Mail from Paul David, Project Manager, to Ruby Wu, the assigned reviewer in OGD.

class labeling actions regarding BRAE's, discontinuation symptoms, and effects of third trimester use on neonates.

From a clinical perspective, this application may be approved with the appended revisions to labeling.

Gregory M. Dubitsky, M.D.
January 5, 2004

cc: NDA #21-519
HFD-120 (Division File)
HFD-120/GDubitsky
/TLaughren
/PAndreason
/JWare
/PDavid

4 Page(s) Withheld

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__✓__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Greg Dubitsky
1/5/04 06:13:23 PM
MEDICAL OFFICER

Thomas Laughren
2/3/04 02:26:09 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detailed comments.--TPL