CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-235

MEDICAL REVIEW(S)

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

DATE: April 14, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products (HFD-130)

SUBJECT: Approval action for NDA 22-235 for Luvox (fluvoxamine) in the maintenance treatment of obsessive compulsive disorder (OCD)

TO: File, NDA 22-235
[Note: This memo should be filed with the 6-20-07 original submission of this NDA.]

Background

Luvox (fluvoxamine) was originally approved for OCD on 12-5-94 (NDA 20-243). Solvay, the manufacturer of Luvox, was placed under AIP on 9-24-97, and as part of the consent agreement, NDA 20-243 was withdrawn on 5-14-02. Subsequently, Solvay submitted NDA 21-519 on 6-28-02. This new NDA included new CMC information in response to one of the deficiencies that led to the AIP decision. Solvay was removed from AIP on 4-9-03, thus starting the review clock for NDA 21-519. Solvay requested, for this new NDA, inclusion by reference to the previous NDA of preclinical, biopharmaceutics, and clinical information.

The 6-28-02 submission addressed some, but not all, of the CMC deficiencies. There were still a number of CMC issues that needed resolution prior to final approval, and these were detailed in a **2-9-04 approvable letter**. In addition, the 6-28-02 submission contained segment I and II reproductive toxicology data in the rat submitted in fulfillment of a phase 4 commitment imposed at the time of the original approval. Dr. Fossom from the pharmacology/toxicology group reviewed segment I and II studies and found them acceptable. However, it was noted that there were [redacted] impurities in the drug substance that were above the level of qualification [redacted] and [redacted] impurities/degradants in the drug product that were also above the level of qualification [redacted]. We advised the sponsor that they should either lower the specifications for these impurities to below the levels for qualification, or if not possible, to qualify them (we recommended specific studies). Finally, we asked for several labeling changes and for a commitment to conduct juvenile animal studies post-approval. b(4)

On 5-16-06 the sponsor responded to the 2-9-04 AE letter with the following:
-Responses to the CMC deficiencies
-Dissolution specifications
-Pharm/tox study results to address the qualification issues
-Labeling changes

Although the sponsor had addressed some of the issues detailed in the 2-9-04 AE letter, there remained some issues that needed to be addressed, and these were conveyed in a **second approvable letter on 11-16-06.**

-The CMC responses were reviewed by David Claffey, Ph.D. from ONDQA. The CMC group concluded that the application could be approved except for the unresolved issue of the acceptance criterion from the [redacted] degradant, because the sponsor had not qualified this impurity as requested. In addition, they had several other issues that needed to be addressed. b(4)

-OCP found the proposed dissolution specifications acceptable.

-Linda Fossum, Ph.D. from the pharm/tox group reviewed the new animal data. She concluded that many of the deficiencies have been adequately addressed, however, several remained, including:

-The [redacted] impurity still had to be qualified.

-For the [redacted] impurity, either the specification needed to be lowered to fall below the level needed for qualification, or it needed to be qualified. b(4)

-Greg Dubitsky, M.D. from the clinical group reviewed the revised labeling proposed by the sponsor. Although he found many of the changes acceptable, there remained some issues that had not been adequately addressed, and some new language needed to be added based on changes made to generic fluvoxamine labeling in the interim.

-All of these changes were conveyed in the 11-16-06 approvable letter.

The sponsor provided a complete response to the 11-16-06 AE letter in a 6-20-07 submission, and Luvox was finally re-approved on 12-20-07. However, the 6-20-07 submission also included data from a maintenance study for Luvox in OCD, and the sponsor was required to separate out these data in a separate NDA, i.e., NDA 22-235. In addition to these new data in support of a maintenance claim, this new NDA included revised labeling in the PLR format.

Efficacy Data

Our review focused on study S114.2.09, a randomized withdrawal study in adult patients with OCD who were treated on an open basis with Luvox in a dose range of 100 to 300 mg/day for 10 weeks. "Responders" from this phase, i.e., those whose YBOCS scores diminished by at least 30% from baseline, were eligible for randomization to either continue on their same dose of Luvox or switch to placebo in a 24 week double-blind phase during which patients were observed for "relapse." Relapse was defined as an increase in the YBOCS score of at least 30% from baseline or refusal to continue due to increased OCD symptoms. The primary endpoint was the proportion of responders who relapse during the observation period. This was a US study (6 centers) in which a total of 116 responding patients were randomized (58 per group). It appeared that these patients were in a responder status for an average period of about 4 weeks before randomization. This period of time in a responder status is considerably shorter than our current requirement (i.e., at least 12 weeks), however, that requirement was not established at the time this study was being planned. Thus, we will accept the results of this study, but be clear about the limitations based on the very brief run-in period. The proportions who relapsed were 32% for Luvox vs 55% for placebo (p=0.0136; CMH). Time to relapse (log-rank test) also favored Luvox (p=0.017). Drs. Dubitsky, Bai, and Khin all considered this a positive study, and

I agree. There were no DSI inspectional findings that raised concerns about data integrity for this study.

Safety Data

The safety profile for Luvox in this study was similar to what is the recognized profile for this drug and there were no new safety findings that raised any concerns about labeling or the approvability of this maintenance claim.

Labeling

We have now reached agreement with the sponsor on final labeling in the new PLR format.

Conclusions and Recommendations

All issues have been resolved and I will issue an approval letter with the mutually agreed upon final labeling attached.

cc:
Orig NDA 22-235
HFD-130/DivFile
HFD-130/TLaughren/MMathis/NKhin/GDubitsky/JCliatt

DOC: Luvox_OCD_LT_Laughren_AP_Memo.doc

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/s/

Thomas Laughren
4/14/2008 09:22:20 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-235
Submission Code	N
Letter Date	June 20, 2007
Stamp Date	June 21, 2007
PDUFA Goal Date	April 21, 2008
Reviewer Name	Gregory M. Dubitsky, MD
Review Completion Date	January 18, 2008
Established Name	Fluvoxamine Maleate
Trade Name	Luvox
Therapeutic Class	SSRI
Applicant	Jazz Pharmaceuticals
Priority Designation	S
Formulation	25mg, 50mg, & 100mg Tablets
Dosing Regimen	100-300 mg/day
Indication	Obsessive Compulsive Disorder (maintenance use)
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that this application be approved. A final decision to approve fluvoxamine for maintenance treatment will be contingent on verification of the efficacy results by the statistical reviewer, a satisfactory site inspection report from the Division of Scientific Investigations, and negotiation of labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no recommendations for specific risk management activities.

1.2.2 Required Phase 4 Commitments

No Phase 4 Commitments are recommended from a clinical standpoint.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Luvox (fluvoxamine maleate) was approved for the acute treatment of OCD in adults under NDA 20-243 on 12-5-94. The OCD maintenance program was undertaken to satisfy a Postmarketing Commitment pursuant to that NDA approval action to evaluate the maintenance efficacy of fluvoxamine in adult patients with OCD. This program consists of a single trial, S114.2.09.

1.3.2 Efficacy

Study S114.2.09 enrolled 247 patients with meeting DSM-IV criteria for obsessive compulsive disorder(OCD). Part I of the study entailed single-blind treatment of these patients with fluvoxamine using flexible dosing in the range of 100 to 300 mg/day. Part II of the study randomized 114 responders from Part I to double-blind treatment with either continued fluvoxamine or placebo and followed them for relapse for up to 24 additional weeks.

Results from Part II showed superiority of fluvoxamine over placebo in terms of relapse rate and time to relapse.

Details of the study design, conduct, and results are provided in section 6 below.

1.3.3 Safety

An abbreviated review of the safety data from study S114.2.09 was conducted. This review focused on identifying any unexpected serious adverse events that would change the existing safety profile of fluvoxamine. No such events were found.

A more comprehensive safety review was not attempted because the study design did not produce the controlled safety data needed for most standard safety analyses. This is not considered a major obstacle to the approval of this application since there are extensive clinical trial and postmarketing spontaneous report safety data with fluvoxamine that have been previously reviewed.

1.3.4 Dosing Regimen and Administration

Dosing during study S114.2.09 was identical to that utilized in the pivotal studies which formed the basis for approval of the acute indication (100 to 300 mg/day, with doses over 100 mg/day given on a divided basis).

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted in support of this application.

1.3.6 Special Populations

Studies in special populations were not performed as part of this program.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Luvox (fluvoxamine maleate) is a selective serotonin reuptake inhibitor (SSRI) that was approved by the Agency for the acute treatment of obsessive-compulsive disorder (OCD) in adults on 12-5-94 under NDA 20-243. Prior to that time, it had been widely marketed worldwide for several years, primarily for the treatment of major depression.

b(4)

2.2 Currently Available Treatment for Indications

In addition to fluvoxamine, four drugs are currently approved for the acute treatment of OCD in the U.S.: Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), and Anafranil (clomipramine). However, only two of these agents, Paxil and Zoloft, have been approved for maintenance treatment of OCD.

2.3 Availability of Proposed Active Ingredient in the United States

Fluvoxamine has been available in the United States since 1995 as the innovator product (Luvox) and, over the past several years, as generic formulations.

2.4 Important Issues With Pharmacologically Related Products

Significant risks associated with the use of SSRI's are:

- increased suicidal ideation and behavior (suicidality) in children, adolescents, and young adults.
- serious reactions, resembling neuroleptic malignant syndrome, when MAOI's are used concomitantly.
- serotonin syndrome when other serotonergic agents, such as other SSRI's, SNRI's, and triptans, are used concomitantly.
- abnormal bleeding, particularly upper gastrointestinal bleeding which may be potentiated when NSAID's or aspirin are used concomitantly.
- hyponatremia, especially in the elderly.

2.5 Presubmission Regulatory Activity

Luvox was approved by the Agency for the acute treatment of OCD on 12-5-94 under NDA 20-243. At that time, the sponsor, Solvay Pharmaceuticals, committed to conduct an adequate and well-controlled relapse prevention study in patients with OCD. Such a trial (Study 114.2.09) was conducted between January 1996 and November 2000 to satisfy this postmarketing commitment.

Subsequently, Solvay 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. Generic formulations of fluvoxamine were permitted to remain on the market.

Solvay then submitted NDA 21-519, which comprised Chemistry, Manufacturing and Controls (CMC) and biopharmaceutics data, with all clinical safety and efficacy data incorporated by reference to the withdrawn NDA, in order to obtain approval to again market Luvox for the acute treatment of OCD. On 4-9-03, Solvay was removed from AIP and the review of NDA 21-519 commenced. That application was granted approval on 12-20-07.

This application was filed as a separate NDA since Luvox was not approved for marketing at that time. This NDA 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" and contains proposed labeling to describe the results of this study in Luvox labeling. It should be noted that the submitted labeling was not formatted in

accordance with the Physician's Labeling Rule (PLR). PLR labeling was subsequently requested from the sponsor.

2.6 Other Relevant Background Information

Postsubmission regulatory activity is summarized below.

A Refuse-to-File (RTF) meeting was held on 8-16-07. It was concluded that this application is fileable and this decision was communicated to the sponsor in a letter dated 8-28-07. That letter also conveyed a number of requests for further clinical and statistical information that is needed to complete the review of this application, including labeling in PLR format.

A Mid-Cycle Meeting was held on 11-30-07. Two issues were discussed:

1) the handling of nine protocol violators for purposes of the statistical analysis. Five of these patients did not meet the criteria for response in Part I of the study and should not have been randomized in Part II but were randomized nonetheless. The other four patients met response criteria in Part II but were excluded from the Part II efficacy ITT sample. See section 6.1.4 for further discussion of this issue.

2) computations performed by the sponsor revealed that the mean time in continuous responder status prior to randomization was 3.7 weeks for patients randomized to fluvoxamine and 4.0 weeks for patients randomized to placebo. These durations are well below the current requirement for three months of clinical stabilization prior to randomization in maintenance trials. Since this study was conducted from 1996 to 2000, prior to the establishment of this requirement, Dr. Thomas Laughren, DPP Director, stated that we would not reject the study for this reason. He indicated that labeling [redacted] in describing the study results, it would mention that patients were in responder status for approximately four weeks, and it state that the results demonstrated a "maintenance" effect at four weeks.

b(4)

On 12-28-07, we were notified that the ownership of this NDA (as well as NDA 21-519) was transferred from Solvay to Jazz Pharmaceuticals, Inc.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Biometrics

The final biometrics review is pending at this time. The statistical reviewer is Steve Bai, Ph.D. There are no known outstanding statistical issues at this time.

3.2 Division of Scientific Investigations

The final inspection report from the Division of Scientific Investigations (DSI) is pending at this time.

3.3. Chemistry

The chemistry review is pending completion at this time. The chemistry Team Leader, Dr. Tom Oliver, indicated that there are currently no chemistry issues of concern.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data were derived from the study report for Study 114.2.09 as well as Case Report Forms (CRF's) from this trial, both submitted on 8-3-07. These data were supplemented by additional information requested in our 8-28-07 letter to the sponsor, which was sent to us on 10-2-07. Those data included time in response status prior to randomization, mean time to relapse, and influence of gender and age on relapse.

4.2 Tables of Clinical Studies

This application contains only one clinical trial, Study 114.2.09, which evaluated the effect of fluvoxamine in preventing relapse in adult outpatients with OCD who responded to acute treatment with fluvoxamine. This study consisted of a 10-week single-blind treatment phase (Part1) followed by a 6-month randomized, double-blind, placebo-controlled phase (Part 2) in responders at the end of Part 1. Fluvoxamine doses in the range 100-300 mg/day were administered using a flexible dose regimen throughout. A total of 247 patients with OCD were enrolled in Part 1 and 116 patients were randomized in Part 2 (58 to drug and 58 to placebo). Thirty-three fluvoxamine and 25 placebo patients completed Part 2.

4.3 Review Strategy

This review entailed an examination of the efficacy results from Study 114.2.09, an assessment of important safety findings from this study (serious adverse experiences and adverse events that led to premature discontinuation), and a evaluation of the labeling revisions proposed by the sponsor to describe these findings in Luvox labeling. Given the limited utility of the safety data derived from the sole clinical trial comprising this application and the extent of previous safety experience with fluvoxamine, a more comprehensive safety review was not conducted.

4.4 Data Quality and Integrity

On 8-30-07, DSI was formally consulted to conduct inspections at the following two centers from Study 114.2.09:

- Center 4 (Dr. Taylor, Middleton, WI).
- Center 6 (Dr. Yaryura-Tobias, Great Neck, NY).

The final DSI inspection report is pending at this time.

In addition, I conducted two audits of the data contained in this application on 1-4-08:

- an audit of the accuracy of adverse event information in Narrative Summaries and line listings vis-à-vis the Case Report Forms (CRF's).
- an audit of the sponsor's coding of investigator (verbatim) adverse event terms to COSTART preferred terms.

The results of the adverse event coding audit are discussed in section 7.1.5.2. The results of the CRF audit are discussed in section 7.2.8.

4.5 Compliance with Good Clinical Practices

Study 114.2.09 was conducted in compliance with the Helsinki Declaration (as revised in 1989) and applicable Good Clinical Practices.

Additionally, Solvay certified that it did 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.

4.6 Financial Disclosures

Michael F. Hare, Assistant Director for Regulatory Affairs at Solvay Pharmaceuticals, certified that he has acted with due diligence to obtain the information required under 21 CFR 54.4 and it was not possible to do so. He states that study S114.2.09 was conducted from 1996 to 2000 and the applicable regulations requiring this information went into effect in February 1999. Unfortunately, Solvay did not request this information from the clinical investigators at the time of the study.

Solvay attempted to collect financial disclosure information from investigators and subinvestigators for this trial by mailing requests for financial disclosure statements. Those not responding were sent a second request. This information could not be obtained.

The sponsor does state that no investigator was a full-time or part-time employee of Solvay Pharmaceuticals at the time of the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

This application contains no new information pertaining to the pharmacokinetic characteristics of fluvoxamine.

5.2 Pharmacodynamics

This application contains no new information regarding the pharmacodynamic properties of fluvoxamine.

5.3 Exposure-Response Relationships

Study 114.2.09 utilized a flexible dosing regimen throughout. Thus, there are no data regarding a dose- or exposure-response relationship of fluvoxamine in the treatment of patients with OCD.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

The maintenance claim for Luvox in the treatment of adult patients with OCD is based entirely on data from study S114.2.09.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in study S114.2.09 was the proportion of acute responders to Luvox who relapsed following during randomized, double-blind treatment with Luvox versus placebo.

One weakness of the above endpoint is that time to relapse is not considered. For example, the proportion of relapses could be equal for drug and placebo but patients randomized to drug may have relapsed considerably later than the placebo patients. Thus, a more commonly utilized efficacy endpoint in studies of this type is time to relapse as measured by the log-rank comparison of Kaplan-Meier survival curves after randomization of acute drug responders to continued active drug versus placebo. Therefore, this latter endpoint was also be examined in the review of the results from this trial.

6.1.3 Study Design

Investigators
This study was conducted at six U.S. sites by the following investigators:

- Steven Rasmussen, MD, Providence, RI.
- Delbert Robinson, MD, Glen Oaks, NY.
- David Tolin, MD, Philadelphia, PA.
- Leslie Taylor, MD, Middleton, WI.
- Wayne Goodman, MD, Gainesville, FL.
- Jose Yaryura-Tobias, MD, Great Neck, NY.

Study Objective

The objective of this trial was to demonstrate the efficacy of fluvoxamine in preventing relapse in subjects with OCD who had shown an adequate acute response.

Study Description

The study consisted of a two-week single-blind placebo run-in/screening phase, ten weeks of single-blind fluvoxamine treatment (Part I), then six months of randomized, double-blind treatment with fluvoxamine or placebo (Part II).

It was planned that 300 patients would enter Part I. Patients had to be at least age 18 years, and have had a diagnosis of OCD by DSM-IV criteria for at least 12 months. A minimum total score of 18 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was required at the end of screening. This roughly corresponds to moderate symptomatology. Axis I conditions that were not secondary to OCD were exclusionary. Also, patients deemed to be at serious suicide risk or who had displayed auto-aggressive behavior during the present episode were to be excluded. Patients requiring continuation of other therapy for OCD (e.g., cognitive behavioral therapy) were not eligible.

In Part I, fluvoxamine was started at a dose of 50mg qHS and increased in 50mg increments every seven days as tolerated to achieve an optimal therapeutic response. The target dose range was 100 to 300 mg/day, with doses over 100 mg/day given in two divided doses. Clinic evaluations were conducted on day 1 (baseline) and at the end of weeks 2, 4, 6, 8, and 10. Part I responders were defined as those patients with Y-BOCS scores at least 30% lower than baseline at the end of weeks 8 and 10. These patients were then eligible to enter Part II.

In Part II, patients were randomized to either fluvoxamine or placebo for an additional six months of therapy. For those randomized to placebo, placebo was gradually substituted for active drug over a two week period to avoid abrupt withdrawal from fluvoxamine. Patients were assessed every two weeks for the first eight weeks and then every four weeks for the duration of the six month period. Relapse was defined as an increase in the Y-BOCS score of at least 30% over the baseline for Part II or patient refusal to continue treatment due to a substantial increase in OCD symptoms. Patients meeting relapse criteria were to be discontinued from the study.

Efficacy Analysis Plan

The intent-to-treat (ITT) efficacy sample was comprised of patients who took at least one tablet of study drug, had a Part II baseline assessment, and had at least one assessment

while on study drug in Part II. The protocol-specified primary efficacy measure was the proportion of patients who relapsed in Part II. This would be analyzed using the Cochran-Mantel-Haenszel test stratified by center. A non-key secondary variable was the time to relapse which would be examined by Kaplan-Meier curve analysis.

6.1.4 Efficacy Findings

Subject Disposition

A total of 247 patients enrolled in Part I, of which 116 (47%) completed this phase; of these. Among the 131 patients who discontinued from part I, the most common reasons for discontinuation were ineffectiveness (23%) and adverse events (14%).

A total of 116 patients were randomized in Part II (58 to fluvoxamine and 58 to placebo). Response criteria were met by 113 patients from Part I. However, the sponsor indicates that five patients not meeting response criteria were inadvertently randomized in Part II in addition to the 113 responders. But also four patients who met response criteria were excluded from the ITT since two had no efficacy assessments on double-blind therapy and another two were not randomized. Thus, 114 patients (113-4+5) comprised the ITT sample used in the sponsor's primary efficacy analysis; 56 were randomized to fluvoxamine and 58 to placebo.

The handling of these nine protocol violators for purposes of the statistical analysis was discussed at the Mid-Cycle Meeting. Regarding the five non-responders from Part I who were randomized to treatment and analyzed as part of the ITT in Part II, it was decided that the degree of deviation from responder criteria would be evaluated for each patient and a sensitivity analysis would be performed by the statistical reviewer to exclude only those patients with clinically meaningful deviations from responder criteria. I examined the data for these five patients on 12-4-07 and it was determined that one of these patients (91019), although a non-responder in a strict sense, had Part I scores close enough to the responder cut-off to be reasonably considered a responder and be included in the ITT sample. A second patient (92043) appeared to meet the responder criteria and likewise should be included in the ITT. The remaining three patients (91038, 91042, and 96049) were to be excluded from the reanalysis ITT. In the case of the four Part I responders who were excluded from the Part II ITT, two of the four responders were randomized to treatment but not included in the ITT because no post-randomization efficacy scores were available. The other two responders were not randomized or treated in Part II of the trial. It was decided that it was appropriate to exclude these four responders from the ITT sample, as was done in the sponsor's analysis.

Of the 116 patients randomized in Part II, 58 (50%) completed the study (33 fluvoxamine and 25 placebo patients). Table 1 below displays the number of efficacy ITT patients in-study by visit during Part II. Relapse was the most common reason for discontinuation overall, occurring in approximately 12% of fluvoxamine patients and 41% of placebo patients. Three fluvoxamine and one placebo patient discontinued due to adverse events. In addition, three fluvoxamine and one placebo patient discontinued due to protocol violations.

Table 1: Patients In-Study by Visit (Double Blind Phase, Efficacy ITT)									
	Week								
	10	12	14	16	18	22	26	30	34
Fluvox.	56	56	52	47	45	38	37	35	33
Placebo	58	58	53	48	43	31	29	27	25

Baseline Characteristics

For Part II, there were no significant differences between the fluvoxamine and placebo groups in terms of age, gender, or ethnicity. The mean age was about 39 years with only one patient in each group age 65 or older. Males comprised about 45% of the fluvoxamine group and 52% of the placebo group. Over 90% of the patients in each group were Caucasian.

The mean total Y-BOCS scores at the beginning of Part II were similar between treatment groups: 13.6 in the fluvoxamine group and 12.9 in the placebo group. There were more patients rated as markedly ill on the CGI-severity scale in the fluvoxamine group compared to placebo (8.9% vs. 3.5%). The fluvoxamine group had a longer duration of the current episode of OCD illness than the placebo group (15.6 vs. 12.9 years) as well as a longer duration of OCD illness overall (24.5 vs. 23.0 years). For both groups, the pattern of illness was generally chronic with symptomatic waxing and waning (in 65% of fluvoxamine and 55% of placebo patients).

The time in continuous responder status prior to randomization is displayed in Table 2 below. Times were comparable between the two treatment groups.

Table 2: Time (weeks) in Continuous Responder Status Prior to Randomization		
	Fluvoxamine	Placebo
N	56	58
Mean (s.e.)	3.7 (0.27)	4.0 (0.28)
Median	4.0	4.0

Dosing Information

Mean doses in the safety ITT during the single-blind phase ranged from 78.2 mg/day at week 2 (N=239) to 135.4 mg/day at week 10 (n=134).

Mean doses in the fluvoxamine group during the double-blind phase were generally in the range of 130 to 135 mg/day. Among the 34 patients in the safety ITT at the study endpoint (week 34), the mean fluvoxamine dose was 130.8 mg/day.

Concomitant Treatments

The most commonly used concomitant drugs during double-blind treatment were Advil and Tylenol in the fluvoxamine group and ibuprofen, Tylenol, and Tylenol Cold in the placebo group. I examined the listing of all medications used concomitantly during Part

II of the study (Table 17 in the study report) and found none with known anti-OCD effects that could have biased the therapeutic response..

Primary Efficacy Results

Table 3 below displays the number of patients who relapsed by treatment group and visit during the double-blind phase (Part II). The difference in the proportions of patients who relapsed at the study endpoint (week 34) was statistically significant: 32% (18/56) in the fluvoxamine group and 55% (32/58) in the placebo group; p=0.0136.

Table 3: Number of Patients Experiencing Relapse (Double-Blind Phase)

	Statistic	Week								
		10*	12	14	16	18	22	26	30	34
Fluvoxamine										
Relapsed	N for that period	0	2	4	3	5	1	3	0	0
	Cumulative	0	2	6	9	14	15	18	18	18[+]
Placebo										
	N for that period	0	3	10	8	5	4	2	0	0
	Cumulative	0	3	13	21	26	30	32	32	32

*End of single-blind phase

[+]p = 0.0136 versus placebo

The sponsor also examined the influence of demographic factors (gender and age) on the cumulative proportion of patients who relapsed by the study endpoint. These data are summarized in Table 4 below. Formal statistical testing on these results was not performed but visual inspection indicates that, within each gender and age stratum, the proportion of fluvoxamine patients who relapsed was substantially less than that among the placebo patients.

Table 4: Effect of Gender and Age on Cumulative Relapse (Double-Blind Phase)

	Fluvoxamine		Placebo	
	N/n[1]	% Relapse	N/n	% Relapse
GENDER				
Male	8/25	32%	14/30	47%
Female	10/31	32%	18/28	64%
AGE				
<50 yrs	13/42	31%	27/50	54%
≥50 yrs	5/14	36%	5/8	63%

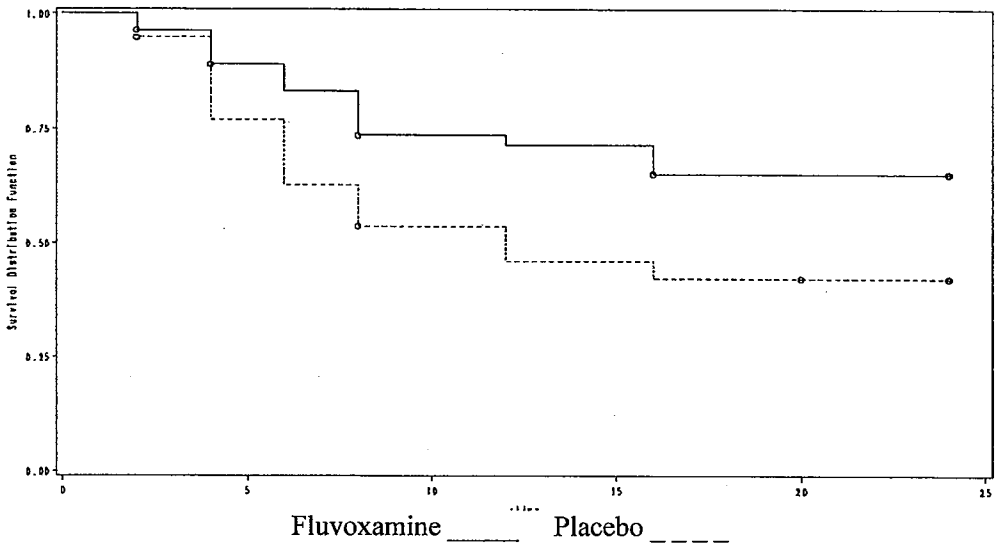
Secondary Efficacy Results

The Kaplan-Meier analysis of relapse demonstrated a significantly lower rate of relapse in the fluvoxamine group versus placebo during the double-blind portion of this study. The survival curves are displayed in Figure 1 below. The mean times to relapse were

[1] N=number of patients with relapse in stratum, n=total number of patients in stratum.

13.2 weeks for fluvoxamine and 10.7 weeks for placebo. This difference was statistically significant (p=0.017 based on the log-rank test).

Figure 1: Kaplan-Meier Relapse Curves (Double-Blind Phase)



Fluvoxamine _____ Placebo _ _ _ _

FDA Sensitivity Analysis

As discussed above, I conducted a sensitivity analysis to exclude 3 patients (91038, 91042, and 96049) who were non-responders but who were nonetheless randomized and included in the sponsor's ITT sample. The status of these patients is summarized as follows:

Patient #	Treatment Group	Relapsed?
91038	Fluvoxamine	No
91042	Placebo	Yes
96049	Fluvoxamine	No

Excluding these three patients from the primary efficacy analysis, the proportion of patients relapsing was 33% (18/54) in the fluvoxamine group and 54% (31/57) in the placebo group. This difference was statistically significant (p=0.0262).

6.1.5 Efficacy Conclusions

Study S114.2.09 demonstrates that fluvoxamine is superior to placebo in maintaining a response in patients who have been clinically stable for approximately four weeks.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in study S114.2.09.

7.1.2 Other Serious Adverse Events

A serious adverse events (SAE) was any event that suggested a significant hazard, contraindication, side effect, or precaution and included any event that was fatal or life-threatening, permanently disabling, required or prolonged hospitalization, or was a congenital anomaly, cancer, or overdose.

Adverse events classified as serious were reported by seven patients who received fluvoxamine: six during single-blind treatment and one during the double-blind phase. A line listing of these patients and SAE's is presented in Table 5 below.

Table 5: Fluvoxamine Patients with Serious Adverse Events

Patient #	Age	Sex	Serious Adverse Events
SINGLE-BLIND PHASE			
91005	38	M	Increased OCD, depression.
92016	32	M	Threatening behavior, agitation (cocaine-associated).
95016	32	M	Back pain, back surgery.
96006	35	M	Mania, psychomotor agitation.
96007	31	F	Suicidal ideation, alcohol abuse.
96051	73	F	Urinary tract infection, E. Coli sepsis.
DOUBLE-BLIND PHASE			
92029	28	M	Gastroenteritis, increased WBC count.

The Narrative Summary for each patient was reviewed by the undersigned. I did not judge any of these events to represent a clinically significant, new event attributable to fluvoxamine therapy.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Tables 6 and 7 below display the numbers of patients dropping out of the single-blind phase and the double-blind phase, respectively, by reason for dropout.

Less than 50% of the enrolled patients completed the single-blind treatment phase. The most common reason for dropout during this phase was ineffectiveness (23%). About 14% discontinued due to an adverse event.

In the double-blind phase, 57% of the fluvoxamine patients in the safety ITT and 43% of the placebo patients completed planned treatment. Fluvoxamine patients most commonly discontinued for reasons classified as "Other," which mostly represented withdrawn consent. Relapse was the most common reason for dropout in the placebo group. It is noteworthy that apparently a number of patients (11 in the fluvoxamine group and 8 in the placebo group) experienced relapse during the double-blind phase but did not dropout; by protocol, these patients should have been discontinued from the study.

Table 6: Single-Blind Phase Discontinuations by Reason	
	Fluvoxamine (N=247)
Completed Phase	116 (47%)
Discontinued due to:	
Ineffectiveness	56 (23%)
Adverse Event	34 (14%)
Lost to Follow-up	16 (6%)
Protocol Violation	13 (5%)
Other (mostly withdrawn consent)	12 (5%)

Table 7: Double-Blind Phase Discontinuations by Reason		
	Fluvoxamine (N=58)	**Placebo (N=58)**
Completed Study	33 (57%)	25 (43%)
Discontinued due to:		
Adverse Event	3 (5%)	1 (2%)
Lost to Follow-up	4 (7%)	2 (3%)
Protocol Violation	3 (5%)	1 (2%)
Relapse	7 (12%)	24 (41%)
Other (mostly withdrawn consent)	8 (14%)	5 (9%)

7.1.3.2 Adverse events associated with dropouts

Adverse events that led to dropout in at least 1% of patients during the single-blind phase are depicted in Table 8 below. Other events leading to premature discontinuation during this phase (by COSTART preferred term) were back pain, palpitations, anorexia, constipation, diarrhea, dyspepsia, flatulence, tooth disorder, alcohol intolerance, agitation, amnesia, anxiety, psychotic depression, dizziness, dry mouth, hyperkinesia, hypertonia, decreased libido, manic reaction, nervousness, paresthesia, somnolence, thinking abnormal, tremor, yawning, sweating, amblyopia, vision abnormal, urinary frequency, and impotence.

Table 8: Incidence of Dropouts due to Adverse Events (Single-Blind Phase)	
	Fluvoxamine (N=241)
Asthenia	4%
Headache	2%
Nausea	2%
Insomnia	2%
Abnormal ejaculation	2%
Depression	1%

All adverse events that led to discontinuation during double-blind treatment with fluvoxamine are presented in Table 9.

Table 9: Incidence of Dropouts due to Adverse Events (Double-Blind Phase)[2]		
	Fluvoxamine (N=57)	**Placebo (N=58)**
Headache	2%	0%
Dizziness	2%	0%
Insomnia	2%	0%
Somnolence	2%	0%
Menstrual disorder[3]	3%	0%

Additionally, one patient (#91023) was discontinued after ten weeks of single-blind fluvoxamine and one week of double-blind fluvoxamine (50 mg/day) due to a low WBC count (3,010/mm^3; normal range 4,800-10,800) and low hemoglobin (13.3 g/dL; normal range 14.0-18.0) discovered at the beginning of the double-blind phase; there were no associated clinical events reported. These abnormalities persisted without worsening nine weeks after discontinuing drug and were considered by the investigator as unlikely related to fluvoxamine. I am inclined to agree with that assessment.

I did not consider any of the adverse events that led to premature discontinuation to alter the existing safety profile of fluvoxamine therapy.

7.1.3.3 Other significant adverse events

My examination of the adverse event verbatim terms in Subject Listings 23 and 24 in the report for study S114.2.09, which contain all adverse events from Part I and II, respectively, revealed no other significant adverse events.

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[2] Two additional events, vertigo and strabismus, were each reported to have led to dropout in one placebo patient.

[3] Delayed menses.

7.1.4 Other Search Strategies

No special searches were performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were either volunteered by the patient or observed by the investigator. The requirement to capture this information was not dependent on an assessment that the event was causally by the study drug.

7.1.5.2 Appropriateness of adverse event characterization and preferred terms

The sponsor's coding of verbatim adverse event terms to COSTART preferred terms was audited by examination of Subject Listings 23 and 24 in the report for study S114.2.09. My comparison of the verbatim and preferred terms for all patients in these two listings revealed no significant coding errors or deficiencies.

7.1.5.3 Incidence of common adverse events

Common adverse event reporting rates from study S114.2.09 will not be discussed in this review since they cannot be meaningfully interpreted. The single-blind phase of the study was uncontrolled and the adverse event reporting rates from the double-blind portion were biased by the preceding single-blind treatment with fluvoxamine.

7.1.6 Less Common Adverse Events

Subject Listings 23 and 24 in the report for study S114.2.09 were examined by the undersigned to detect any adverse event verbatim terms that might suggest a less common but clinically significant adverse event that is attributable to fluvoxamine and not previously associated with fluvoxamine treatment. No such events were found.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This application contains only one clinical trial: Study S114.2.09 was a randomized withdrawal study consisting of a 10 week single-blind fluvoxamine treatment phase in patients with OCD (Part I) followed by randomization of responders to either continued fluvoxamine therapy or placebo under double-blind conditions for an additional 24 weeks

(Part II). Part I enrolled 247 patients; 116 patients were randomized in a 1:1 ratio in Part II.

7.2.1.2 Demographics

Demography of the patients from study S114.2.09, the single study in this application, is discussed in section 6.1.4 above.

7.2.1.3 Extent of exposure (dose/duration)

Data regarding mean dose stratified by duration of exposure were not provided by the sponsor. Data regarding the number of patients in-study over time and mean doses during double-blind treatment are discussed in section 6.1.4 above.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

This is a single-study application.

7.2.2.2 Postmarketing experience

No postmarketing safety data were submitted as part of this application.

7.2.2.3 Literature

No literature search was submitted in this application.

7.2.3 Adequacy of Overall Clinical Experience

In my opinion, the submitted safety and efficacy data are sufficient to render a judgement regarding the approvability of this application.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal or *in vitro* test data were provided in this application.

7.2.5 Adequacy of Routine Clinical Testing

The clinical monitoring performed during study S114.2.09 was adequate to detect any clinically significant adverse events emerging during fluvoxamine therapy.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No pharmacokinetic data or interaction studies were conducted to support this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Study S114.2.09 permitted adequate evaluation of serious adverse events associated with fluvoxamine during the study. Although the design of this trial does not allow for evaluation of the rates of common adverse events, rare adverse events, or changes in vital sign, laboratory test variables, or ECG parameters with longer-term fluvoxamine versus placebo use, studies which would permit adequate examination of these measures are rarely practical given the need for substantial retention of subjects in-study over prolonged periods of time and a placebo control. Thus, no further study is recommended.

7.2.8 Assessment of Quality and Completeness of Data

Adverse event safety data were audited for completeness and accuracy in a 5% (N=2) sample of submitted Case Report Forms (CRF's).[4] Adverse events from the CRF's for these patients were compared to those discussed in the corresponding Narrative Summaries and those listed in Subject Listings 23 (single-blind phase) and 24 (randomized, double-blind phase) in the report for study S114.2.09. No deficiencies or discrepancies were noted.

The results of the DSI inspections are pending at this time:

7.2.9 Additional Submissions, Including Safety Update

No Safety Update is required since this application involves a single study that has been completed.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The nature of the adverse event data from study S114.2.09 does not permit an identification of common drug-related adverse events. No less common events of a more serious nature were identified that would alter the safety profile of fluvoxamine.

In sum, there were no safety findings that would preclude approval of Luvox for longer term use in the treatment of adult patients with OCD or require prominent labeling.

[4] Patients 114209-02-92010 and 114209-06-96051.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The target dose for maintenance therapy is identical to that for acute treatment of OCD (100-300 mg/day, with doses over 100 mg/day given on a divided basis).

8.2 Drug-Drug Interactions

This application contains no new information on drug-drug interactions.

8.3 Special Populations

This application contains no new information on the use of fluvoxamine in special populations.

8.4 Pediatrics

This application contains no new information on the use of fluvoxamine in the pediatric population.

8.5 Advisory Committee Meeting

No advisory committee meeting is planned for this application.

8.6 Literature Review

No literature review was conducted in support of this application.

8.7 Postmarketing Risk Management Plan

No specific postmarketing risk management plan is required for this application.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

Study S114.2.09 provides an adequate demonstration of the efficacy of fluvoxamine in maintaining response in patients with OCD who responded to fluvoxamine and had been clinically stable for an average of about four weeks. There were no safety findings that would preclude approval or require prominent labeling.

It is very doubtful that this approval will have any appreciable impact on clinical practice given the short (4 week) period of stabilization prior to randomization and the fact that the two studies which provided the basis for the initial U.S. approval of fluvoxamine for OCD were 10 weeks in duration. Nonetheless, I have no objection to approving this application as long as labeling clearly states that maintenance was shown after about four weeks of stabilization [redacted] b(4)

9.2 Recommendations on Regulatory Action

From a clinical perspective, it is recommended that this application be approved. A final decision to approve fluvoxamine for maintenance treatment will be contingent on verification of the efficacy results by the statistical reviewer, a satisfactory site inspection report from the Division of Scientific Investigations, and negotiation of labeling.

9.3 Recommendations on Postmarketing Actions

9.3.1 Risk Management Activity

There is no recommendation for any specific risk management activity.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 Commitments.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests recommended.

9.4 Labeling Review

In accordance with guidance from the Clinical Team Leader, Dr. Ni Khin, this labeling review was based on the Solvay labeling provided in the 8-3-07 submission and focused on those clinical sections directly pertinent to the maintenance claim supported by study S114.2.09. A more comprehensive labeling review for purposes of creating final labeling will be conducted by the review team at a later date after the new sponsor, Jazz Pharmaceuticals, submits revised labeling in accordance with the Physician's Labeling Rule.

CLINICAL PHARMACOLOGY/Clinical Trials/Adult OCD Maintenance Study
The description of study S114.2.09 should be revised to define Part I responders, remove

[redacted] b(4)

[redacted] b(4)

In the double-blind phase, patients receiving continued LUVOX experienced, on average, a significantly lower relapse rate [redacted] than those receiving placebo.

An examination of population subgroups from this trial did not reveal any clear evidence of a differential maintenance effect on the basis of age or gender.

INDICATIONS AND USAGE

This section requires two revisions: 1) the discussion of effectiveness for long-term use should be deleted and replaced by presentation as a maintenance effect after four weeks of clinical response and 2) the mention of the DSM-III-R definition of OCD in the first paragraph should add DSM-IV since patients in study S114.2.09 were diagnosed by DSM-IV criteria for OCD.

The following text is suggested for this section:

LUVOX Tablets are indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in the DSM-II-R or DSM-IV.

OCD is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

[redacted] b(4)

[redacted] b(4)

ADVERSE REACTIONS/Incidence in Controlled Trials/Commonly Observed Adverse Events in Controlled Trials

[redacted] b(4)

DOSAGE AND ADMINISTRATION/Maintenance/Continuation Extended Treatment

[redacted] I recommend replacing the proposed language with the following text for consistency with other recently approved applications for other drugs with a similar indication:

> **Maintenance Treatment**
> It is generally agreed that obsessive compulsive disorder requires several months or longer of sustained pharmacologic therapy. The benefit of maintaining patients with OCD on LUVOX after achieving a response for an average duration of about 4 weeks was demonstrated in a controlled trial. (See Clinical Trials under CLINICAL PHARMACOLOGY.) The physician who elects to use LUVOX for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

9.5 Comments to Applicant

There are no clinical comments to the sponsor.

10 APPENDICES

10.1 Review of Individual Study Reports

See above discussion of study S114.2.09 in section 6 above.

10.2 Line-by-Line Labeling Review

A line-by-line labeling review was not conducted at this time. See section 9.4.

REFERENCES

None.

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

/s/

Greg Dubitsky
1/18/2008 02:27:47 PM
MEDICAL OFFICER

Ni Aye Khin
2/19/2008 06:44:39 PM
MEDICAL OFFICER
I agree with Dr. Dubitsky's recommendations. See also memo to file for additional comments.