# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-235**

# SUMMARY REVIEW

**MEMORANDUM**

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

**DATE:** February 19, 2008

**FROM:** Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products

**TO:** File NDA 22-235 (This overview should be filed with the 06-20-2007 submission.)

**SUBJECT:** Recommendation of Approval Action for Luvox (fluvoxamine) for the Maintenance Treatment of Obsessive-Compulsive Disorder (OCD)

## 1. BACKGROUND

Luvox (fluvoxamine) is a selective serotonin reuptake inhibitor (SSRI). It was originally approved in the U.S. on 12/5/94 under NDA 20-243 for the acute treatment of Obsessive Compulsive disorder (OCD) at doses up to 300 mg per day.

The manufacturer, Solvay was placed under the Application Integrity Policy (AIP) by the Agency in September 1997 mostly for CMC issues. As part of the agreement to remove from the AIP, Solvay withdrew NDA 20-243 on 05/14/02.

On 06/28/2002, NDA 21-519 was submitted with new CMC information while preclinical, clinical pharmacology and clinical study information were included as reference to the previous NDA. The Agency issued an approvable letter on 2/9/04 detailing CMC issues needed to be addressed prior to approval. On 5/16/06, the sponsor responded to the 2004 AE letter. The Agency then issued a second AE letter on 11/16/06 citing outstanding CMC, dissolution and labeling issues. The sponsor submitted their response to the 2006 AE letter on 6/21/07 in which they included a claim for Luvox in maintenance treatment of OCD based on results from study S114.2.09. This maintenance claim was filed as a separate NDA (NDA 22-235) since Luvox was not approved for marketing at that time.

On 12/20/2007, Luvox is approved on for its use in the acute treatment of OCD under NDA 21-519. The approved dosing regime is 100 to 300 mg/day, with doses over 100 mg/day given on a divided basis. Luvox tablets are available in 25, 50 and 100 mg strengths. Recently, there was a transfer of ownership of this drug from Solvay to Jazz Pharmaceuticals.

Currently, Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), and Anafranil (clomipramine) are labeled for treatment of OCD in addition to Luvox (fluvoxamine). Among these drugs, Paxil and Zoloft have been approved for maintenance treatment of OCD.

This NDA has been reviewed by Greg Dubitsky, M.D., Medical Officer, DPP (review dated 1/18/2008) and Steve Bai, Ph.D., from the Office of Biostatistics (review dated 2/14/2008).

On 1/30/08, the sponsor submitted the labeling changes in new PLR format under this NDA. Carol Noory from the Office of Clinical Pharmacology provided the PLR labeling review in her memo dated 2/15/2008.

## 2.0 CHEMISTRY

No new CMC issue in this NDA. CMC information was cross-referenced to NDA 21-519 which was previously reviewed by Dr. David Claffey from ONDQA. I am not aware of any CMC issues that would preclude approvability of this NDA.

## 3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues that would require a review.

## 4.0 CLINICAL PHARMACOLOGY

There was no OCP issues submitted that would require a review. OCP recommends minor changes in the Warning/Precautions (5.9) and drug interactions (7.11) sections.

## 5.0 CLINICAL DATA

### 5.1 Efficacy Data

#### 5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of a single study (study S114.2.09) to evaluate the efficacy and safety of fluvoxamine in the maintenance treatment of OCD.

#### 5.1.2 Summary of Study Pertinent to Efficacy Claim

Study S114.2.09

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. The study enrolled patients who were 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 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).

In Part I, fluvoxamine was started at a dose of 50 mg at bedtime and increased in 50 mg 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. 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.

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

The study was conducted at 6 U.S. centers. A total of 247 patients were enrolled in the Part I of the study. Of these 247 patients, 131 subjects discontinued; the most common reasons for discontinuation were ineffectiveness (23%; 56 subjects) and adverse events (14%; 34 subjects). A total of 116 patients continued in the study at the end of the Part I and were randomized to receive either fluvoxamine or placebo (58 subjects in each group) in the Part II of the study. A total of 58 subjects (50%) which comprised of 33 fluvoxamine and 25 placebo patients completed the study. Relapse was the most common reason for discontinuation in this Part II, occurring in 12% of fluvoxamine and 41% of placebo patients.

The subjects enrolled were mostly Caucasian (92%); mean age of 39 yrs. Male comprised about 45% of the fluvoxamine group and 52% of the placebo group. There seemed to be no significant differences in demographic characteristics among the treatment groups. The mean total YBOCS scores at the beginning of Part II were similar between the treatment groups: 13.6 in the fluvoxamine group and 12.9 in the placebo group.

It appeared that patients were stabilized (meeting responder status) for approximately four weeks prior to randomization into the double-blind phase. Mean doses of fluvoxamine 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 was in the range of 130 to 135 mg/day.

The protocol-specified primary efficacy measure, the proportion of patients who relapsed in Part II, was analyzed using the **Cochran-Mantel-Haenszel** test stratified by center. Dr. Bai confirmed the efficacy results. 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** (see Table 3 in Dr. Dubitsky's clinical review for detailed results).

Although time to relapse, a more commonly utilized efficacy endpoint in studies of this type, was not a key secondary variable in this study, this was also examined by using Kaplan-Meier analysis.

The mean times to relapse were **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.

Drs. Bai and Dubitsky stated in their reviews that sensitivity analysis was conducted by excluding data from 3 patients (91038, 91042, and 96049) who were non-responders but were randomized and included in the sponsor's ITT sample. The reanalysis retained statistically significant results in favor of Luvox.

Comment: Both Drs. Dubitsky and Bai considered this a positive study for fluvoxamine, and I agree with them.

### 5.1.3 Comments on Other Important Clinical Issues

Subgroup analyses
Exploratory subgroup analyses was performed in order to detect subgroup interactions on the basis of gender (M, F), and age (<50 yrs, ≥50 yrs). Overall results seem to indicate that the proportion of relapse was less in the fluvoxamine patients (31-36%) than that among the placebo (47-64%) patients within each gender and age stratum (see Table 2 in Dr. Dubitsky's clinical review for detail). No subgroup analysis on race was performed because the majority of study subjects (92%) were Caucasian.

Dose response relationship
This study was a flexible dose study. The target dose range was 100 to 300 mg/day. Mean doses in the fluvoxamine group during the double-blind phase was generally in the range of 130 to 135 mg/day.

### 5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of S114.2.09 supported the maintenance efficacy claim of fluvoxamine in the treatment of OCD patients who have been clinically stable for approximately four weeks.

## 5.2 Safety Data

As stated by Dr. Dubitsky in his review, the safety review of this NDA is limited to the safety findings from this study S114.2.09 with primary assessment focused on serious adverse experiences and adverse events that led to premature discontinuation. Common adverse event reporting rates were not evaluated in his review since they cannot be meaningfully interpreted based on the study design. Part I enrolled 247 patients; 116 patients were randomized in a 1:1 ratio in Part II.

There was no death reported in study S114.2.09. Serious adverse events were reported by seven patients who received fluvoxamine: six during single-blind treatment and one during the double-blind phase. The detailed list of SAE can be seen in Table 5 in Dr. Dubitsky's clinical review. The events included increased OCD, depression, agitation, back surgery, mania, suicidal ideation, infection and increased WBC count. The AE dropout rates during the double-blind phase were 5% in fluvoxamine group and 2% in the placebo group. The AEs that led to discontinuation listed headache, dizziness, insomnia, somnolence and menstrual disorder.

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) at the beginning of the double-blind phase. These lab abnormalities persisted without worsening nine weeks after discontinuing fluvoxamine.

### 5.2.1 Conclusion Regarding Safety Data

Overall, this NDA submission revealed no new or specific safety concerns that would preclude approval of fluvoxamine (Luvox) in the maintenance treatment of adult patients with OCD.

## 6.0 WORLD LITERATURE

No literature review was conducted in support of this NDA. I am not aware of any specific safety concerns with Luvox recently published in the literature.

## 7.0 FOREIGN REGULATORY ACTION

The sponsor did not provide any foreign regulatory action information regarding maintenance use of Luvox CR in OCD.

## 8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

## 9.0 DSI INSPECTIONS

Inspections were conducted at 2 U.S. study sites (Dr. Taylor, Center 4 and Dr. Yaryra-Tobias, Center 6). I am not aware of any inspectional findings that would impact integrity of study data.

## 10.0 LABELING AND ACTION LETTER

### 10.1 Final Draft of Labeling Attached to the Action Package

The sponsor has provided labeling in new PLR format. The sponsor's proposed language for maintenance OCD claim should be modified. All the labeling changes should be negotiated with the sponsor. A copy of final agreed-upon labeling should be included in the action letter.

## 11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to demonstrate a longer time to relapse comparing fluvoxamine to placebo in the maintenance treatment of OCD. While I note Dr. Dubitsky's concerns regarding determination of the length of stabilization period during the open-label treatment with fluvoxamine based on the study design, I agree with his recommendation that we should describe the benefit of maintaining patients with OCD on therapy after achieving a responder status for an average duration of about 4 weeks in the clinical trials section of the

labeling. I recommend we consider approval of this NDA provided that we reach an agreement with the sponsor regarding the language in the labeling.

cc: HFD-130/Laughren/Mathis/Dubitsky/Grewal

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/s/

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MEDICAL OFFICER