CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 28, 2008

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

SUBJECT: Recommendation for approval action for Luvox CR (fluvoxamine extended release) for social anxiety disorder (SAD) and obsessive compulsive disorder (OCD)

TO: File NDA 22-033
[Note: This overview should be filed with the 12-28-07 response to the agency's 12-20-07 second approvable letter for this NDA.]

1.0 BACKGROUND

Luvox CR (fluvoxamine extended release) is an extended release formulation of fluvoxamine, an SSRI that is approved in an immediate release form for the treatment of OCD. This NDA seeks claims for the short-term treatment of social anxiety disorder (SAD) and obsessive compulsive disorder (OCD), in a dose range of 100 to 300 mg/day, given qd. The studies supporting this claim were conducted under IND 57,838, and a pre-supplemental NDA meeting was held with the sponsor on 9-22-04 to discuss CMC and biopharmaceutics issues.

This NDA was originally submitted 5-1-06, and the first approvable letter was issued 2-27-07. The sponsor came back with a complete response on 6-21-07 and, as noted, we issued a second approvable letter on 12-20-07. There were essentially two remaining issues to be resolved, i.e., dissolution specifications and establishing an expiry. The sponsor quickly responded on 12-28-07 with a complete response to these issues, including a request for a meeting to discuss these deficiencies.

We met on 1-22-08 for a premeeting to discuss the remaining deficiencies. Our 2-27-07 AE letter had identified a dissolution range of → at the 6 hour time point. Although the sponsor accepted the proposed dissolution specifications, including those at the 6 hour time point, the problem was that there would be an unacceptable failure rate of manufacturing lots for

such a strict range at 6 hours, making it impossible to set a reasonable expiry. [Note: A slightly more generous range of ——, or even ——, would have allowed all lots to pass, but this was not acceptable to OCP.] The CMC group appeared to find 6 hour limits of —— acceptable, or ——, or indeed dropping the 6 hour limits altogether. It should be noted that the accepted 4 hour limits are —— and the accepted 8 hour limits are —— Thus, it is unfathomable from a clinical standpoint how limits for the 6 hour time point are an issue at all. Consequently, the clinical group opted to drop the requirement for 6 hour limits. The CMC group found this acceptable, and the sponsor has accepted the revised specifications without a 6 hour requirement.

2.0 CHEMISTRY

All of the CMC issues have been resolved, including the issue of extablishing an expiry date (see discussion under Background above).

3.0 PHARMACOLOGY

Early in the review process, there was an impurity issue that was an obstacle for the final approval of both NDA 21-519 for the sponsor's IR formulation of fluvoxamine and for this NDA for Luvox CR. This issue has now been resolved as of the last review cycle. The sponsor has committed to providing further information on a 14-day toxicity study during phase 4.

4.0 BIOPHARMACEUTICS

The only remaining issue for the biopharm group was the matter of dissolution specifications, and as noted under Background, I have recommended a slight modification of the limits that I find clinically acceptable and this makes it possible to reasonably manufacture a product that, in my view, is fully acceptable.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were 3 double-blind, randomized, parallel-group, flexible-dose, placebo-controlled, short-term (12 weeks) efficacy and safety trials in this program. Two of these studies (3107 & 3108) evaluated Luvox CR in adult outpatients with SAD in a dose range of 100 to 300 mg/day, and one study (3103) evaluated Luvox CR in adult outpatients with OCD in a dose range of 100 to 300 mg/day. The primary endpoint for the SAD studies was change from baseline to endpoint in

the LSAS total score, and the primary endpoint for the OCD study was change from baseline to endpoint in the Y-BOCS total score. All 3 studies were positive for Luvox CR on the primary endpoint.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

There was no information pertinent to dose/response for efficacy in this program.

Secondary Efficacy Variables

The sponsor proposed to [redacted]

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, as there were not sufficient data to conduct explorations based on age and race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive SAD and OCD trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy for SAD and OCD in this supplement. However, [redacted], and the sponsor has agreed to conduct a randomized withdrawal study with Luvox CR in SAD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of Luvox CR in the treatment of SAD and OCD. As noted, they will be permitted to include in labeling information only for the primary endpoint in these trials. The sponsor has agreed to conduct a pediatric SAD study and a maintenance study in SAD. We will not request a

pediatric OCD trial under PREA, because the sponsor has already conducted a pediatric OCD trial for immediate release fluvoxamine.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review and Overview of Findings

The safety data for this supplement were derived from a total of n=614 subject and patients exposed to Luvox CR across the 11 clinical trials comprising this program (6 phase 1 pk studies, the 3 phase 3 safety and efficacy trials, and 2 extension trials). The observed common adverse events profile was consistent with that seen with the immediate release formulation for this drug.

5.2.2 Conclusions Regarding Safety

The adverse event profile for Luvox CR in the treatment of SAD and OCD is quite similar to that seen for fluvoxamine IR for its approved indications, and can be adequately characterized in labeling. Some problems were noted in the coding and analysis of safety data by the sponsor, however, these have now been resolved.

5.3 Clinical Sections of Labeling

We made a number of modifications to the sponsor's proposed labeling, and have now reached agreement with the sponsor on final labeling.

6.0 WORLD LITERATURE

The sponsor was not able to find any literature references that were specific to fluvoxamine CR. Dr. Dubitsky (who helped in the evaluation of the safety data for this application) was able to identify 3 such references, referring to studies conducted as part of this program, and none revealed any new safety information that would change conclusions about the approvability of this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Luvox CR is not approved anywhere at this time.

8.0 DSI INSPECTIONS

Inspections were conducted at 6 sites, and data from all 6 were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling

We have now reached agreement with the sponsor on final labeling.

10.2 Foreign Labeling

Luvox CR is not approved anywhere at this time.

10.3 Approval Letter

The approval letter includes agreed upon final labeling and agreements on phase 4 commitments.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Solvay has submitted sufficient data to support the conclusion that Luvox CR is effective and acceptably safe in the treatment of SAD and OCD. I believe we have satisfactorily resolved the remaining issues identified in our 12-20-07 approvable letter, and we have reached agreement with the sponsor on final labeling. Thus, I will issue an approval letter.

cc:
Orig NDA 22-033
HFD-130
HFD-130/TLaughren/MMathis/GZornberg/RGrewal

DOC: LuvoxCR_OCD_SAD_Laughren_AP_Memo.doc

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

/s/

Thomas Laughren
2/28/2008 08:00:36 AM
MEDICAL OFFICER