CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-519

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: November 16, 2006

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

SUBJECT: Approvable action for NDA 21-519 for Luvox (fluvoxamine) in the treatment of obsessive compulsive disorder (OCD)

TO: File, NDA 21-519
[Note: This memo is in reference to the 5-16-06 response to our 2-9-04 approvable letter for this NDA.]

Luvox (fluvoxamine) was originally approved for OCD on 12-5-94. 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the manufacturer of Luvox, was placed under AIP on 9-24-97, and as part of the consent agreement, NDA 20-243 was withdrawn on 5-14-02.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 remaining 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 ▬ impurities in the drug substance that were above the level of qualification (0.15%) and ▬ impurities/degradants in the drug product that were also above the level of qualification (0.20%). 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). b(4)

Finally, we asked for several labeling changes and for a commitment to conduct juvenile animal studies post-approval.

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 has addressed some of the issues detailed in the 2-9-04 AE letter, there remain some issues that need to be addressed, and these will be conveyed in a second approvable letter.

The CMC responses were reviewed by David Claffey, Ph.D. from ONDQA. The CMC group has concluded that the application can 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 they would like 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 concludes that many of the deficiencies have been adequately addressed, however, several remain, including:

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

-For the [redacted] impurity, either the specification needs to be lowered to fall below the level needed for qualification, or it needs 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 remain some issues that have not been adequately addressed, and some new language needs to be added based on changes made to generic fluvoxamine labeling in the interim. All of these changes will be conveyed in the new approvable letter.

Conclusions and Recommendations: I agree with the review team that this NDA is not yet ready for approval. Instead, we will be issuing a second approvable letter that details the remaining CMC and pharm/tox deficiencies that must be addressed prior to final approval.

cc:
Orig NDA 21-519
HFD-130/DivFile
HFD-130/TLaughren/MMathis/NKhin/GDubitsky/WBender

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/s/

Thomas Laughren
11/16/2006 01:23:03 PM
MEDICAL OFFICER

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 3, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 21-519 for Luvox (fluvoxamine) in the treatment of obsessive compulsive disorder (OCD)

TO: File, NDA 21-519
[Note: This memo is in reference to the 6-28-02 original submission of this NDA.]

Luvox (fluvoxamine) was originally approved for OCD on 12-5-94. 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.

CMC: This NDA has been reviewed by Lorenzo Rocca, Ph.D., and to my understanding, all CMC deficiencies have been fully addressed.

Biopharmaceutics: This NDA has been reviewed by Andre Jackson, Ph.D. As noted, Solvay requested re-instatement of all biopharmaceutics information, including bioequivalence data linking the clinical materials used in the clinical trials with the TBM formulations. One problem was that the numbering of the studies as listed in the new NDA was different than that used in the original NDA. Thus, this issue needed to be clarified, and it was, revealing that these were the same studies originally reviewed. OCPB also sought and received confirmation that the formulations now being proposed are identical to those originally approved, the manufacturing procedures and sites are identical, and the dissolution specifications and methods are also identical. Thus, OCPB has concluded that there are no remaining biopharmaceutical issues to be resolved.

Clinical: Dr. Dubitsky has reviewed several matters for this NDA:
-He looked at safety data for 2 of the 3 bioequivalence studies linking clinical study and TBM formulations, apparently not realizing that these were not new studies, but rather, studies that had been included in the original NDA. In any case, he concluded that no new safety information was revealed.

-He concluded that financial disclosure was acceptable.
-He concluded that a pediatric waiver was acceptable, since the only age group missed by the previous study was age 7.
-He recommended adding information to labeling regarding standard language for all SSRIs and also an addition to the NMS Warning statement that Solvay had previously requested.
-Thus, he concluded that this NDA is approvable, pending acceptance of our proposed labeling.

Conclusions and Recommendations: I agree that this NDA is approvable, and I recommend we issue an approvable letter, along with the labeling proposed by Dr. Dubitsky.

cc:
Orig NDA 21-519
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PAndreason/GDubitsky/PDavid

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/s/

Thomas Laughren
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