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: September 16, 2002

FROM: Thomas P. Laughren, M.D.
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HFD-120

SUBJECT: Recommendation for Non-Approval Action for Pediatric Supplement for Celexa (Citalopram); negative results for Celexa in the treatment of Major Depressive Disorder (MDD) in pediatric patients

TO: File NDA 20-822/S-016
[**Note:** This overview should be filed with the 4-18-02 original submission of this supplement.]

1.0 BACKGROUND

Citalopram is a selective serotonin reuptake inhibitor that is approved for the treatment of MDD in adults. Supplement 016 includes data from 2 safety and efficacy trials of citalopram in pediatric patients with MDD, and also data from 2 pediatric PK studies. This supplement was submitted in support of pediatric labeling for Celexa in the treatment of MDD. Although only one of the 2 clinical trials supported the efficacy of citalopram in MDD, the sponsor has proposed labeling that characterizes the results of the positive study, and also provides safety information and PK information.

It should be noted that, at this time, there are no drugs approved for the treatment of pediatric MDD.

It should be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they were given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request.

Since the proposal was to use the currently approved Celexa formulations for this expanded population, there was no need for chemistry or pharmacology reviews. The primary review of the clinical efficacy and safety data was done by Earl Hearst, M.D. from the clinical group. Since there was agreement between the sponsor and FDA that these trials were negative, there was no need for a statistics review of the efficacy data. The data from the PK study were reviewed by Vanitha Sekar, Ph.D., from OCPB.

The original supplement for this expanded indication (S-016) was submitted 4-18-02. There was no safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Celexa is a marketed product, there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Celexa is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

This supplement provided results of PK studies CIT-PK-07 and CIT-PK-13.
-CIT-PK-07: This was a multiple dose study in n=13 pediatric patients (10-17) and n=12 adults (21-45), given citalopram 20 mg qd, for 1 week, followed by 40 mg qd, for 3 weeks. PK parameters were similar in the 2 groups (adolescents and adults).
-CIT-PK-13: This was a single dose study in n=12 children (7-11) and n=12 adults (18-35), given citalopram 20 mg. Children had a greater overall exposure, compared to adults given the same dose (AUC 1/3 higher), and Cmax about 20% higher.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Studies CIT-MD-18 and 94404

5.1.1.1 Study CIT-MD-18

This was an 8-week, randomized, double-blind, parallel group, placebo-controlled, flexible dose, multicenter trial (21 US centers) in child (ages 7-11) and adolescent (ages 12-17) outpatients with MDD (DSM-IV). Randomization was stratified between these 2 age groups. Citalopram dosing was flexible, in a range of 20 to 40 mg/day, on a qd basis. For the first 4 weeks, the maximum dose was 20 mg, but the dose could be increased to 40 mg during the last 4 weeks, as needed and tolerated. The primary outcome was change from baseline on the total CDRS-R (first 17 items). The primary analysis was ANCOVA (LOCF), for the ITT population as usually defined.

The total randomized sample was n=174 (citalopram=89, placebo=85). The sample was about 50% females, about 80% Caucasian, and the mean age overall was about 12, with roughly equal proportions in the 2 age strata. Information on the mean citalopram dose for completers at endpoint was not available at the time of completing this memo. The ITT samples were identical to the randomized samples. The proportions completing to 8 weeks were as follows: citalopram-80%; placebo-79%. The results on the primary outcome were as follows:

Efficacy Results on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R	[P-value(vs pbo)]
Citalopram	**58.8**	**-21.7**	**0.038**
Placebo	**57.8**	**-16.5**	

The efficacy results broken out by children and adolescents are as follows (the sponsor did not calculate p-values for these groups separately):

Efficacy Results (Children) on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R
Citalopram	**60.0**	**-20.9**
Placebo	**56.8**	**-17.1**

Efficacy Results (Adolescents) on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R
Citalopram	**57.5**	**-22.6**
Placebo	**58.6**	**-15.4**

Thus, it appears that the positive results for this trial overall are coming largely from the adolescent subgroup.

Note: There was a packaging error resulting in tablets being distinguishable for drug and placebo for 9 patients (although still blinded). A re-analyses without these patients yielded a p-value of 0.52 in favor of citalopram.

Results also significantly favored citalopram over placebo on most secondary outcomes.

Comment: I agree with Dr. Hearst that this is a positive study in support of the efficacy of citalopram in pediatric MDD.

5.1.1.2 Study 94404

This was an 12-week, randomized, double-blind, parallel group, placebo-controlled, flexible dose, multicenter trial (31 non-US centers) in adolescent (ages 13-18) outpatients with MDD (DSM-IV).

Citalopram dosing was flexible, in a range of 10 to 40 mg/day, on a qd basis. Dosing began at 10 mg for the first week, but could be increased to 20 mg for week 2, 30 mg for weeks 3 and 4, and up to a maximum dose of 40 mg thereafter, as needed and tolerated. The primary outcome was change from baseline on the total score for the Schedule for Affective Disorders and Schizophrenia for School Aged Children (Kiddie-SADS-P). The primary analysis was a repeated measures ANCOVA (OC), for the ITT population as usually defined.

The total randomized sample was n=244 (citalopram=124, placebo=120). The sample was about 75% females, 100% Caucasian, and the mean age overall was about 16. Information on the mean citalopram dose for completers at endpoint was not available at the time of completing this memo. The ITT samples were as follows: citalopram=115; placebo=108. The proportions completing to 12 weeks were as follows: citalopram-65%; placebo-66%. The results on the primary outcome were as follows:

Efficacy Results on Kiddie-SADS-P Total Score for Study 94404 (OC)

	Mean Baseline K-SADS	Mean O baseline K-SADS	[P-value(vs pbo)]
Citalopram	**32.5**	**-12.4**	**0.791**
Placebo	**32.3**	**-12.7**	

The results were equally negative on secondary outcomes.

Comment: This is a clearly negative study that provides no support for the efficacy of citalopram in pediatric patients with MDD.

5.1.2 Conclusions Regarding Efficacy Data

The results for study 18 are positive, but the results for study 94404 are clearly negative. The doses used were comparable to doses that have shown efficacy in adults, and the PK data from these studies suggest that the exposures should have been adequate. Thus, underdosing does not seem a likely explanation for the failure of study 94404. Thus, they have submitted only 1 positive study, and that is not sufficient, in my view, to support a claim for MDD in pediatric patients. I agree with Dr. Hearst that no efficacy findings should be mentioned in labeling.

5.2 Safety Data

The pediatric safety data for citalopram in this supplement came from the 2 placebo-controlled efficacy studies (18 and 94404), and the two PK studies (07 and 13), yielding a total of 259 pediatric patients exposed to this drug (roughly 1/4 children and 3/4 adolescents). Although there are longer-term safety data being collected in pediatric patients, these data were not submitted as part of this supplement. The safety profile for citalopram in this population was similar to that seen in adults. Of note, in study 18, there was a mean change in weight of 0 for citalopram vs an increase in 1.4 pounds for placebo. Weight data were not reported for study 94404.

5.3 Clinical Sections of Labeling

The sponsor's proposed labeling for this supplement included a number of additions: (1) pediatric PK information under Clinical Pharmacology, Pharmacokinetics; (2) a summary of the positive study under Clinical Pharmacology, Clinical Efficacy Trials; (3) a reference to pediatric efficacy data in Indications and Usage; (4) a reference to efficay, safety, and PK information under Precautions, Pediatric Use; (5) a reference to pediatric safety under Adverse Reactions; and (6) a reference to pediatric use under Dosage and Administration. Dr. Hearst recommended that no changes be made to labeling, and I agree. As I have indicated, I feel these mixed efficacy findings (one positive and one negative study) are essentially uninterpretable, since we know that, in adults, studies in MDD, even if fully adequate on face and for drugs that we know to be effective, fail to discriminate the active drug from placebo about half the time. Since there were no unexpected safety findings, I also agree that nothing regarding safety needs to be added. Finally, in the absence of convincing efficacy findings, I agree that there is no good reason to characterize the PK in this population, since this may encourage use of citalopram.

6.0 WORLD LITERATURE

No literature pertinent to the use of citalopram in pediatric patients was provided in this supplement.

7.0 FOREIGN REGULATORY ACTIONS

I am not aware of any foreign regulatory actions regarding the use of citalopram in pediatric patients.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

Since there was agreement with the sponsor that one of the two studies was clearly negative, we did not request DSI inspections.

10.0 NON-APPROVAL LETTER

An non-approval letter acknowledging our decision not to add and information to labeling regarding the use of citalopram in pediatric MDD has been included with the non-approval package.

11.0 CONCLUSIONS AND RECOMMENDATIONS

As I have discussed under section 5.3, it is my view that none of the efficacy results of this negative program for citalopram in pediatric MDD should be noted in labeling, nor is there any reason to add information regarding the safety or pharmacokinetics of citalopram. Thus, I recommend that we issue the attached nonapproval letter indicating our view that labeling should not be altered based on the findings submitted with this supplement.

cc:
Orig NDA 20-822/S-016
HFD-120/Division File
HFD-120/TLaughren/RKatz/EHearst/PDavid

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/s/

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MEDICAL OFFICER