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: March 19, 2009

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

SUBJECT: Recommendation for Approval Action for Lexapro (escitalopram) tablets and solution as monotherapy for the acute and maintenance treatment of major depressive disorder (MDD) in adolescent patients

TO: File NDA 21-323_S-030/031 and NDA 21-365_S-021/022
[Note: This overview should be filed with the 5-22-08 original submissions of these supplements.]

1.0 BACKGROUND

Lexapro (escitalopram), the S-enantiomer of citalopram, is an SSRI that is approved (1) as monotherapy for the acute and maintenance treatment of MDD in adults, and (2) as monotherapy for the acute treatment of GAD in adults. This supplement provides data in support of claims for Lexapro for acute monotherapy and maintenance monotherapy of MDD in adolescent patients. These studies were conducted under IND 58,380. There is currently only one other drug approved for the treatment of pediatric MDD, i.e., fluoxetine.

The sponsor's proposed dose range for Lexapro in adolescent MDD is 10 to 20 mg/day.

The primary review of the efficacy and safety data was done by Roberta Glass, M.D., from the clinical group. George Kordzakhia, Ph.D., from the biometrics group, also reviewed the efficacy data. These supplements included labeling for Lexapro in PLR format for the first time. This new labeling format required review by all disciplines. In addition, this revised labeling was reviewed by the Maternal Health Team (MHT).

We decided not to take these applications to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

Lexapro is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a request for categorical exclusion was made and accepted.

3.0 PHARMACOLOGY

Lexapro is an approved product. There were no pharm/tox issues that required review as part of these supplements, other than for labeling in the PLR format.

4.0 BIOPHARMACEUTICS

Lexapro is an approved product. The sponsor included data from 3 pharmacokinetic studies in pediatric patients as part of these supplements, and these data were reviewed by Andre Jackson from OCP. They also reviewed the sponsor's proposed label. OCP concluded that no dose adjustment is needed in adolescents, compared to adults, and had no comment on the sponsor's proposed label.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor needed 2 positive short-term efficacy trials to support a claim for pediatric MDD, and in prior discussions, we had agreed that it would be sufficient to provide data from 1 positive study with Lexapro. We agreed to extrapolate on the basis of a previously reviewed positive study with citalopram (Study CIT-MD-18).

Overall, the sponsor submitted data from 3 Lexapro studies pertinent to its new claims in adolescent MDD, including from 2 short-term studies (Studies SCT-MD-32 and SCT-MD-15) and from a double-blind, controlled extension study (Study SCT-MD-32A). They were seeking both an acute and a maintenance claim in adolescent MDD. As noted, they also referenced Study CIT-MD-18, and I will also briefly summarize a fifth short-term citalopram study, i.e., 94404. All of these trials were flexible-dose and none included an active control arm.

Acute Monotherapy Studies

-Study SCT-MD-32: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (escitalopram 10-20 mg/day), 8-week trial in adolescent outpatients (ages 12-17)

meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the CDRS-R total score. Escitalopram was statistically significantly superior to placebo (Pbo: -18.4; escit: -22.4; p=0.022).
-Study CIT-MD-18: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (citalopram 20-40 mg/day), 8-week trial in pediatric outpatients (ages 7-17) meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the CDRS-R total score. Citalopram was statistically significantly superior to placebo (Pbo: -16.5; cit: -21.7; p=0.038). While this study was positive overall, the effect size was greater for the adolescent subgroup compared to the child subgroup (7.2 units on the CDRS-R for adolescents vs 3.8 for children).
-Study SCT-MD-15: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (escitalopram 10-20 mg/day), 8-week trial in pediatric outpatients (ages 6-17) meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the CDRS-R total score. Escitalopram was not statistically significantly superior to placebo (Pbo: -20.3; escit: -20.9; p=0.31). The adolescent sample in this study was slightly larger (n=160; p=0.233) than the child sample (n=104; p=0.875).
-Study 94404: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (citalopram 20-40 mg/day), 8-week trial in adolescent outpatients meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the Kiddie-SADS_P total score. Citalopram was not statistically significantly superior to placebo. Thus, this was another negative study.

Maintenance Study (SCT-MD-32A)

This was not a randomized withdrawal study, as is usually the case with a study proposed as a basis for a maintenance claim. Rather, Study 32A was a double-blind, placebo-controlled 16-week extension of responders from Study 32. As such, it violated randomization, and we do not consider it interpretable. Thus, I will not comment further on the results from this study.

5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

These were all flexible-dose studies, thus, there is no basis for assessing dose response for efficacy.

Key Secondary Endpoints

CGI was prespecified as a key secondary endpoint in both studies 32 and 18. Although escitalopram was superior to placebo on the CGI in Study 32 (p=0.008), this was not the case for Study 18 (b) (4)

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the CDRS-R were similar to effect sizes seen in other positive pediatric MDD trials.

Duration of Treatment

Although we do not consider Study 32A to be a reasonable basis for assessing maintenance efficacy, we have been willing to extrapolate from adult maintenance data when both acute and maintenance efficacy have been established in adults and acute efficacy has been established. I am willing to make such an extrapolation to pediatric patients in this case as well.

PMR Study in Children with MDD

Although the sponsor has provided some data from the 7-11 age group, I do not feel they have adequately explored efficacy in this subgroup. The effect size in the 7-11 age subgroup in Study 18 is actually about the same as that seen in the positive escitalopram study (32), but the sample size may have been too small to show statistical significance. It is very likely that patients in the 7-11 age group will be treated with Lexapro, even in the absence of sufficient data. We cannot require an efficacy study in the 7-11 age group under PREA or under FDAAA. We discussed this issue with the sponsor, and they were not willing to commit to another efficacy study in children. However, they do plan to conduct an open label safety study in children with MDD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support a claim for the acute treatment of MDD in adolescent patients, and I am willing to extrapolate maintenance efficacy for adults with this condition to adolescent depression.

5.2 Safety Data

There were no unexpected or unusual safety findings that would impact on labeling or an approval action for this application.

5.3 Clinical Sections of Labeling

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

6.0 WORLD LITERATURE

The literature review did not reveal any unexpected or unusual safety findings that would impact on labeling or on an approval action for this application.

7.0 FOREIGN REGULATORY ACTIONS

Lexapro is not approved for any pediatric indications in any other countries.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

These applications were not take to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at two sites that enrolled patients from study 32. The data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

As noted, we reached agreement on final labeling.

11.0 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has submitted sufficient data to support the conclusion that Lexapro is effective as acute monotherapy in the treatment of adolescent MDD. We are able to extrapolate maintenance efficacy to pediatric patients from positive data in adults with MDD. The safety profile appears to be similar to that observed with this drug in adults. We have reached agreement on final labeling, and I will issue an approval letter.

cc:
Orig NDAs 22-323_S-030/031/NDA 21-365_S-021_022
HFD-130
HFD-130/TLaughren/MMathis/NKhin/RGlass/RGrewal

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/s/

Thomas Laughren
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MEDICAL OFFICER