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 17, 2009

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: NDA 21-323/SE5-030/031 (tablets)
NDA 21-365/SE5-021/022 (oral solution)
(This overview should be filed with the 05-22-2008 submission.)

SUBJECT: Recommendation of Approval Action for Lexapro (escitalopram) for the Acute and Maintenance Treatment of Major Depressive Disorder (MDD) in Adolescents

1. BACKGROUND

Lexapro (escitalopram), the S-enantiomer of the racemic citalopram, is a serotonin reuptake inhibitor (SSRI). It is approved in the U.S. since 2002, for the treatment of major depressive disorder (MDD) in adults at doses up to 20 mg per day. It is also approved for the treatment of generalized anxiety disorder in adults. The recommended dose is 10 mg daily with dose can be increased to 20 mg/day. Escitalopram tablets are available in 5, 10 and 20 mg strengths. It is also available in oral solution form, 5 mg/ml.

Currently, Prozac (fluoxetine) is approved fro use the pediatric population for the MDD indication. Both Celexa (citalopram) and Lexapro (escitalopram) are approved for acute and maintenance treatment of MDD in adults.

The Agency has received sponsor's submission of the above referenced supplemental NDAs on 5/23/08. The applications included the efficacy and safety results from a positive short-term study with escitalopram (Study SCT-MD-32) in adolescents with MDD. They also included results from Study SCT-MD-32A, a 16-week extension study.

This set of supplemental NDAs has been reviewed by Roberta Glass, M.D., Medical Officer, DPP (review dated 01/29/2009) and George Kordzakhia, Ph.D., Statistical Reviewer, from the Office of Biostatistics (review dated 01/28/2009). An Environmental Assessment Review was conducted by Nallaperum Chidambaram, Ph.D., Chemist, ONDQA (memo dated 09/12/2008).

In this submission, the sponsor has made conversion of the Lexapro labeling to new PLR format. Each discipline was asked to provide any PLR labeling comments during the review cycle. In addition, this set of supplements was chosen by the Maternal Health Team (MHT) from OND as part of their pilot projects for PLR labels and provided some labeling recommendations regarding section 8.1 (Pregnancy) and 8.3 (Nursing Mothers) (in review dated 1/29/2009 by Jeanine Best).

2.0 CHEMISTRY

No new CMC information submitted in this NDA supplement except environmental assessment issues. The applicant had claimed categorical exclusion from submitting an EA document and such claim was found acceptable. In addition, there are no further changes to the proposed PLR labeling from a CMC perspective per Dr. Nallaperum Chidambaram, ONDQA, in his email dated 2/10/2009.

3.0 PHARMACOLOGY/TOXICOLOGY

No new pharmacology/toxicology issues submitted in this supplemental NDA. Dr. Barry Rosloff, Supervisory Pharmacologist, provided some minor PLR labeling edits for the pharmacology/ toxicology sections. He also reviewed PLR labeling recommendations from the MHT. Dr. Rosloff noted that MHT has recommended several changes to section 8.1 (Pregnancy). As suggested by MHT, it was acceptable to have an introductory paragraph followed by an Animal Data section in the PLR label, but it was unacceptable to him that numerous editorial changes to the description of the animal data should be made. (b) (4)

4.0 CLINICAL PHARMACOLOGY

There was no new OCP issues submitted that would require a review. OCP will be providing PLR labeling comments. At the time completing this memo, I have not received their labeling comments yet.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

To fulfill the requirement of positive results from two placebo-controlled studies to support efficacy of pediatric MDD for escitalopram, the division has agreed to accept one positive pivotal study in citalopram Study CIT-MD-18 (Study 18) and one positive study in escitalopram Study SCT-MD-32 (Study 32). Because Study 32 enrolled adolescents only, and the positive efficacy results of Study 18 derived primarily from the adolescent treatment group, the sponsor's intended indication claim is for treatment of MDD in adolescents.

In this review cycle, our review of efficacy was focused on the positive results from one placebo-controlled short-term study (study SCT-MD-32) in our evaluation of the efficacy and safety of escitalopram in the acute treatment of MDD in adolescents.

Study 32 is an 8 week, double-blind, placebo-controlled, flexible dose (escitalopram 10-20 mg/d) study in adolescents (age 12-17 yrs) with MDD. The clinical and statistical reviews covered the

details of study design and findings in this study. I will discuss the efficacy data from this study in the subsection 5.1.2.1 below.

As noted by both Drs. Glass and Kordzakhia in their reviews, I concur that the Study SCT-MD-32 A (hereafter referred as study 32A)**,** a 16 week extension study, would give uninterpretable results due to design flaws. It should not be used to support maintenance efficacy claim.

Study 18 is an 8 week, double-blind, placebo-controlled, flexible dose (citalopram 20-40 mg/d) study in children (7-11 yrs) and adolescents (12-17 yrs). I would refer to the clinical review by Dr. Earl Hearst dated 9/12/02 and a memorandum by Dr. Thomas Laughren dated 9/16/02 regarding their reviews of materials submitted under supplemental NDA for citalopram on 04/18/2002. I will briefly summarize their interpretation of results from the Study 18 in section 5.1.2.3 below.

Two other studies were considered negative and they were not reviewed in detail for efficacy: Study SCT-MD-15 (Study 15), an 8 week, placebo-controlled, flexible dose (escitalopram 10-20 mg/day) study in children and adolescents; and Study 94404, a 12 week, double-blind, placebo-controlled, flexible-dose study (citalopram 10-40 mg/day) in adolescents with MDD.

5.1.2 Summary of Study Pertinent to Efficacy Claim

5.1.2.1 Study SCT-MD-32

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose (escitalopram 10-20 mg/day) study of the safety and efficacy of escitalopram in the treatment of adolescent patients (12-17 years of age) with a DSM-IV diagnosis of MDD.

The study consisted of a 2-week screening period, including single-blind placebo lead-in during the second week, followed by 8 weeks of double-blind treatment. At the end of the single-blind period, eligible patients were randomized 1:1 to one of two double-blind treatment groups (escitalopram or placebo). The escitalopram dosage was 10 mg/day for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/day by the investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7). Patients who completed the 8-week double-blind treatment period were eligible to enter a 1-week double-blind down-taper period or to continue in an extension study for additional 16 weeks (Study SCT-MD-32A).

This study was conducted at 40 study centers in the United States (US). A total of 584 patients were screened for eligibility; 316 patients were randomized to receive either study drug or placebo and 311 patients had at least one post-baseline CDRS-R assessment (ITT Population). A total of 133 (84.2%) placebo patients and 126 (79.7%) escitalopram patients completed 8 weeks of double-blind treatment, and 202 patients (100 placebo, 102 escitalopram) continued into the extension study, SCT-MD-32A. There were 94 subjects discontinued from the study: 52 (37.1%) in the escitalopram and 42 (30%) in the placebo group. Reasons for discontinuation included lack of therapeutic response [5 subjects (3.2%) in each group]; adverse events [4 subjects (2.5%) in escitalopram and 1 (0.6%)]; withdrawal of consent, lost to follow up, protocol violations and others.

The mean patient age was 14.6 years; majority was Caucasian (75%) and females (59%). There were no statistically significant differences between the two treatment groups with respect to demographic characteristics. However, the sponsor stated that there were statistically significant

differences in CDRS-R total score and CGI-S at baseline between the two treatment groups with higher depression severity in the escitalopram group.

All efficacy analyses were performed on the ITT Population. All primary and secondary efficacy analyses were performed using the LOCF approach. The between–treatment group comparison was performed using a two-way analysis of covariance (ANCOVA) model with treatment group and study center as factors and the baseline score as a covariate. A sensitivity analysis for the primary efficacy parameter was performed using the mixed-effects model for repeated measures (MMRM) methodology based on the observed post-baseline longitudinal data. The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline value as covariate. The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. The key secondary efficacy parameter was the CGI-I score.

Dr. Kordzakhia confirmed sponsor's primary efficacy analysis. As can be seen in table 1 below, the change from baseline to Week 8 in the escitalopram group was statistically significantly greater than that in the placebo group. As noted in his statistical review, the findings from the sensitivity analysis, MMRM, support the primary efficacy results.

Table 1: Primary Efficacy Results on Change from baseline in CDRS Total Scores at endpoint (LOCF; ITT population)

Treatment Groups (Total Number =311)	Mean Baseline total CDRS (SD)	LS mean Change from Baseline Mean at endpoint	Placebo adjusted difference (95% CI); p-values (drug vs. placebo)
Escitalopram (N=154)	57.6 (0.7)	-22.4 (1.1)	-3.4 (-6.2, -0.5); p=0.022
Placebo (N=157)	56 (0.7)	-18.4 (1.1)	

Comment: Both Drs. Glass and Kordzakhia considered this a positive study for escitalopram, and I agree with them.

5.1.2.2 Study SCT-MD-32A

As noted by Dr. Glass in her review, Study 32A was originally designed as a 24 week, flexible-dose, open label extension study. After the study began and patient data was collected, the protocol was amended several times to evolve into a double blind, placebo controlled, 16 week extension study. The study design did not allow re-randomization of patient treatment assignment at the beginning of Study 32A after completing Study 32. The study showed almost 75% drop out rate for both treatment groups. I agree with both Dr. Glass and Kordzakhia's comments that the maintenance effect in this study would be confounded with the acute effect. The data for this study was considered uninterpretable.

5.1.2.3 Study CIT-MD-18

Study 18 is an 8 week, randomized, double-blind, placebo-controlled, flexible dose citalopram (20-40 mg/day) study conducted in 160 pediatric patients (aged 7-17) diagnosed with MDD. The treatment groups are stratified for age group (children: 7-11 and adolescents: 12-17). The primary

efficacy variable is the change from baseline to 8 weeks comparing the placebo and citalopram groups on the Children's Depression Rating Scale-Revised (CDRS-R).

A total of 83 children (age 7-11) entered the study; 66 completed the study [citalopram n=36 (80%); placebo n=30/38 (79%)]. A total of 91 adolescents (age 12-17) entered the study; 72 completed the study [citalopram n=35 (79.5%); placebo n=37/47 (79%)]. The mean age in both treatment groups is 12 y.o. with the majority of patient being female (53% for citalopram and 54 % for placebo) and Caucasian (81% and 73%, respectively).

The study was positive for the primary efficacy variable of change from baseline of the CDRS-R total score: citalopram -21.7 $\pm$ 1.6; placebo -16.5 $\pm$ 1.6 (p=0.038). Please see Table 2 in section 5.1.3 regarding summary of primary efficacy results by age group for Study CIT-MD-18 (LOCF data extracted from Dr. Laughren's memo dated 9/16/2002). There seemed a greater improvement for the adolescent group than the children group when comparing the differences to placebo. It also appears that the positive results for this trial were coming largely from the adolescent subgroup.

5.1.2.4 Study SCT-MD-15

This study was a double blind, placebo controlled, 8-week, flexible dose (escitalopram 10-20 mg/day) study in children and adolescents (6-17 yrs) with MDD. This study was conducted at 25 study centers in the United States (US). 264 patients were randomized to receive either escitalopram (n=131) or placebo (n=133); 217 completed the study: escitalopram (n=102), placebo (n=115). Mean age was 12.3 yrs with a subset of adolescents randomized to placebo was 81 and the escitalopram group was 79. The study results did not show any statistical significance for the primary efficacy variable of change from baseline of the CDRS-R total score at week 8: escitalopram -20.3 $\pm$ 1.3; placebo -20.9 $\pm$ 1.2; p=0.084. The study was considered a negative study.

5.1.2.5 Study 94404

This study was a double-blind, placebo-controlled, 12 week, flexible dose (citalopram 10-40 mg/day) study in adolescents with MDD. This study was conducted at 31 international sites. The primary efficacy variable was change from baseline of Kiddie-SADS-P at week 8. This study was also considered a negative study.

5.1.3 Comments on Other Important Clinical Issues

Subgroup analyses on treatment effect

Exploratory subgroup analyses were performed in order to detect subgroup interactions on the basis of gender (M, F), and race (White, African American, others) on the primary efficacy variable, change from baseline in CDRS-total scores at week 8. For all subgroups (except for African American, comprised of a small number [N=24] of patients, did not demonstrate any improvement), the treatment effect appeared to be numerically in favor of escitalopram when compared with placebo in study SCT-MD-32.

As noted before in Dr. Hearst's clinical review and Dr. Laughren's team leader memo, in study 18, subgroup analysis based on age (children: 7-11; adolescents: 12-17 yrs) showed that there was a greater improvement for the adolescents than the children when comparing the differences to

placebo. It appeared that the positive results for this trial were coming largely from the adolescent subgroup (Table 2).

Table 2: Summary of primary efficacy results by age group for Study CIT-MD-18 - LOCF (data extracted from Dr. Laughren's memo dated 9/16/2002)

Age Group	Treatment Groups	Mean baseline CDRS-R Total Score	Mean change from baseline CDRS-R
Children (N=83)	Citalopram (N=45) Placebo (N=38)	60.0 56.8	-20.9 -17.1
Adolescents (N=91)	Citalopram (N=44) Placebo (N=47)	57.5 58.6	-22.6 -15.4

Given these findings, I concur with Dr. Glass that we should ask the sponsor to conduct additional short-term efficacy study in children (age 6-12 yrs) as part of Phase 4 post-marketing requirements. MDD can be reliably diagnosed in this younger age population.

Key secondary efficacy variable

The key secondary efficacy variable established is the CGI-I, a clinician-rated instrument used to rate the total improvement or worsening in a patient's mental illness, based on the Investigator's clinical opinion. Study 32 showed statistically significant difference in change from baseline in favor of escitalopram treatment, compared to placebo using the ANCOVA model for the CGI-I (p=0.008); however, Study 18 with citalopram did not demonstrate statistical significance for this efficacy variable.

(b) (4)

Dose Response Relationship

Study 32 is a flexible dose study of escitalopram 10-20 mg/day. No adequate studies have been conducted to explore dose-response relationship in this patient population.

Duration of Treatment

Although the sponsor intends to have a maintenance claim based on results from the longer-term extension phase study 32A, we have decided that study 32A cannot be used for maintenance claim as it would give uninterpretable results due to design flaws. However, the Division's current policy would allow for maintenance claim in pediatrics based on extrapolation from adult MDD maintenance claim once acute pediatric treatment is established as efficacious.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analysis of study 32 supported the efficacy claim of escitalopram in the acute treatment of MDD in adolescents. Based on prior clinical review by Dr. Hearst and Dr. Laughren's memo, we should be able to count on positive efficacy results from citalopram study 18

in the same aged population for acute treatment of MDD. Maintenance claim in treatment of MDD for the adolescent population is supported by extrapolation from adult data.

5.2 Safety Data

5.2.1 Safety Database

Dr. Glass' safety review of this supplemental NDA included data from escitalopram studies in patients with MDD with the safety data base cut-off date of 12/31/2007. The escitalopram safety data base for treatment of adolescents with MDD includes the following: Study 32, 8 week adolescents (12-17 yrs) study using flexible dose escitalopram (10-20 mg/d) (n=157) vs. placebo (n=155); Study 32A, a longer term, 16 week extension study (24 week total); and Study 15, 8 week flexible dose escitalopram (10-20 mg/d) (n=131 includes 79 adolescents) study in pediatric (6-17 yrs.) patients diagnosed with MDD placebo (n=133 includes 81 adolescents).

The safety update covered the period of 01/08 to 05/2008 regarding the sponsor's review of spontaneous post-marketing adverse events reports.

(b) (4)

A total of 988 pediatric patients received ≥1 dose of study drug; of these, 764 patients were between ages 12-17 yrs and 36 patients aged 18 yrs The sponsor counted a total of 800 adolescent patients in the escitalopram/citalopram safety data base: escitalopram n=234; citalopram n=169 and placebo n=387. A total of 210 patients (181 adolescents) received escitalopram for at least 8 weeks, and 53 patients (all adolescents) received escitalopram for at least 24 weeks; 211 patients (154 adolescents) received citalopram for at least 8 weeks, and 66 patients (30 adolescents) received citalopram for at least 24 weeks. The sponsor concludes that the escitalopram/citalopram safety data base included 83 adolescents who were exposed for up to 24 weeks of escitalopram or citalopram. Doses for escitalopram are either 10 or 20 mg daily. Of the 154 intent-to-treat escitalopram patients in Study 32, 54 patients received 10 mg on their last visit, and 100 patients received 20 mg on their last visit. Overall exposure (in patient years) was 58.7 (all aged groups in 286 escitalopram treated patients) and 51.3 (in 234 adolescents treated with escitalopram).

There was no death reported in the escitalopram safety database review for this submission. Serious adverse events were available from this double-blind phase. In those subjects who experienced SAE, the events included suicidalty (ideation and attempts) and aggravation of depression, and they were identified in both placebo and escitolopram treated groups. The incidence of premature withdrawal was greater in the escitopram group (4.3%) compared to the placebo group (1.3%). The most common AE in dropouts in the escitalopram included insomnia, self injury, fatigue and restlessness.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). Based on the information provided by the sponsor in this application, no AEs terms would meet this definition from the acute studies; UTI from the longer term study. The common AE occurring with greater frequency in the escitalopram compared to placebo in acute studies included headaches, abdominal pain, nausea and insomnia; diarrhea in the longer term study.

5.2.2.2 Vital Signs and Growth Data

In the short term studies (15 and 32) weekly vital sign monitoring included sitting pulse, blood pressure, and weight. Height was recorded at baseline and at study end or early termination. In the longer term study (32A), sitting pulse, blood pressure and weight were measured weekly for the first 5 weeks and then monthly. Orthostasis was assessed in Studies 32 and 32A at baseline and the end of Weeks 1, 6, 10, 12, and 24. There were no clinically significant vital sign change differences (blood pressure and pulse) comparing the placebo and escitalopram groups.

Regarding growth assessment in the pediatric population as determined by use of a z-score (defined by the number of standard deviations from the population mean for a specific subject's weight or height given their age and sex), the sponsor stated that the z-score changes appeared to be similar between treatment groups, indicating that escitalopram did not appear to have an identifiable effect on height and weight change in the study adolescent population. Dr. Kordzakhia has confirmed the sponsor's findings in his statistical review.

5.2.2.3 ECG Data

There were no dropouts due to ECG abnormalities. As stated by Dr. Glass in her clinical review, there were two patients (0091505 and 0303213) with an increased QTc prolongation of > 60 msec; no placebo patients have a clinically significant increase in QTc. The escitalopram patients with an increase from baseline to endpoint in QTc during escitalopram treatment (without significant increase in heart rate): QTcF 2.7$\pm$15.5 ms vs. -0.1$\pm$15.4 in placebo.

The sponsor is conducting a thorough QT study to better characterize the QTc effect of this drug. As proposed by the Agency, the sponsor submitted the protocol, a six-sequence, three-period, cross-study using moxifloxacin as control; and the Agency's QT-IRT had reviewed and provided comments to the sponsor regarding the study design in September, 2008. The Division intends to let current label stand until results from the QT study are received and can be reviewed.

5.2.2.4 Laboratory Tests

There were no significant differences between the escitalopram and placebo groups in mean changes from baseline to endpoint in all laboratory values tested. It was noted that the mean increase for AST was higher in the escitalopram group (0.9$\pm$7 U/L) than in the placebo group (-0.1 $\pm$8.6 U/L).

5.2.2.5 Suicidality Analysis

The sponsor's analysis based on instruments/scales (the Modified Columbia-Suicide Severity Rating Scale and the Suicide Ideation Questionnaire-Junior High School Version) and the incidence of treatment emergent AE potentially associated with suicidal behavior in the escitalopram adolescent safety database was discussed by Dr. Glass in her clinical review, section 7.1.6.

Current escitalopram label contains the standard class suicidality language in the Boxed Warning and the Warnings/Precautions section. The sponsor proposes to use the same language in the PLR label.

5.2.3 Conclusion Regarding Safety Data

Overall, this supplemental NDA submission revealed no new or specific safety concerns. We should continue to monitor and follow up on any post-marketing safety issues with this drug.

6.0 WORLD LITERATURE

The sponsor has provided a literature review in this submission. Based on Dr. Glass' review, the submitted materials indicated some unusual adverse events including tics, EPS, dystonia, oculogyri crisis, Rabbit Syndrome and enuresis. Both Dr. Glass and the sponsor did not raise any specific concerns regarding these AEs with this drug at this time. We should continue to monitor these findings in post-marketing reports for any unconfounding cases.

7.0 FOREIGN REGULATORY ACTION

The sponsor reported that there is no application pending or approved for escitalopram in either pediatric MDD or other pediatric indications in any countries outside the US.

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 study sites (Northwest CRC in Bellevue, WA, and PCSD-Feighner Research in San Diego, CA) participated in study 32. Based on our communication with DSI, DSI did not find any major violations from these two sites that would compromise data integrity. DSI clinical inspection summary is pending.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

This submission contains revised labeling in a new PLR format. We plan to incorporate part of the labeling changes proposed by the MHT, and also, the SEALD team's recommendation when received. I note Dr. Glass' recommendation to include a section in the label entitled "Need for Comprehensive Treatment Program" modeled after the section for stimulant use in ADHD in highlighting drug treatment is one aspect of the effective MDD therapies available for adolescents

with MDD. The sponsor's proposed language in this submission should be modified. All these labeling changes will be negotiated with the sponsor. A copy of final labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to demonstrate that escitalopram is effective and reasonably safe in acute treatment of MDD in adolescents. We should consider for maintenance claim in treatment of MDD for the adolescent population by extrapolation from adult data. I recommend we consider approval of this set of NDA supplements provided that we reach an agreement with the sponsor regarding the language in the labeling. We should ask the sponsor to conduct additional short-term efficacy study in children (6-12 yrs) with MDD as part of post-marketing requirement.

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

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/s/

Ni Aye Khin

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MEDICAL OFFICER