DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-822/S-035
NDA 21-046/S-014
NDA 21-323/S-028/S-029
NDA 21-365/S-018/S-019

Forest Laboratories, Inc.
Attention: Maricarmen Raposo
Associate, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Ms. Raposo:

Please refer to your supplemental new drug applications dated March 20, 2008, received on March 21, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrochloride) tablets (NDA 20-822), Celexa (citalopram hydrochloride) oral solution (NDA 21-046)Lexapro (escitalopram oxalate) tablets (NDA 21-323), and Lexapro (escitalopram oxalate) solution (NDA 21-365), .

We also acknowledge receipt of your submissions dated April 4, 2008 & August 25, 2008.

Your submission of August 25, 2008 constituted a complete response to our January 1, 2008 and August 7, 2008 action letters.

These "Changes Being Effected" supplemental new drug applications provide for class labeling changes to the Precautions, Information for Patients Geriatric Use & Drug Interactions Section of the Labeling:

PRECAUTIONS

Abnormal Bleeding

SSRIs and SNRIs, including [Lexapro/Celexa], may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of [Lexapro/Celexa] and NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

~~Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Celexa/Lexapro treatment. All patients with these events have recovered with discontinuation of Celexa/Lexapro and/or medical intervention.~~
~~Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.~~

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see Geriatric Use). Discontinuation of [Lexapro/Celexa] should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Information for Patients

Patients should be cautioned about the concomitant use of [Lexapro/Celexa] and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Geriatric Use

SSRIs and SNRIs, including [Lexapro/Celexa], have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS**, Hyponatremia).

Drug Interactions

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin) –

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of NSAID or aspirin may potentiate this risk of bleeding. Altered

anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when [Lexapro/Celexa] is initiated or discontinued.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and medication guide).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 20-822/S-035, NDA 21-046/S-014, NDA 21-323/S-028/S-029, NDA 21-365/S-018/S-019**." Approval of these submissions by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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
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