DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-323/S-001
NDA 21-440

Forest Laboratories, Inc.
Attention: Robert W. Ashworth, Ph.D.
Senior Director, Regulatory Affairs
Plaza 3, Suite 602
Harborside Financial Center
Jersey City, NJ 07311

Dear Dr. Ashworth:

Please refer to your new drug applications (NDA) dated October 26, 2001, received October 29, 2001 (NDA 21-440), and August 22, 2002 (NDA 21-323/S-001), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 20 mg Tablets.

Reference is also made to an Agency approval letter dated August 14, 2002, sent to NDA 21-323 providing for the use of Lexapro for the treatment of major depressive disorder.

We acknowledge receipt of your amendments submitted to NDA 21-440 dated December 10, 2001, January 10, and February 28, 2002.

These new drug applications provide for labeling revisions to include prevention of relapse following long-term treatment of major depressive disorder.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling text below. Accordingly, these applications are approved effective on the date of this letter.

We note your agreement to the labeling below in a telephone conversation dated August 29, 2002, between Mr. Paul David, of this Agency, and yourself.

LABELING

Below is the final agreed upon labeling.

1. Under **CLINICAL PHARMACOLOGY-Clinical Efficacy Trials**:

   [The final two paragraphs in the recently approved labeling for Lexapro (i.e., describing the longer-term trials for Celexa) should be deleted, and the following paragraph should be inserted as the final paragraph (i.e., now becoming the third paragraph) in this subsection.]

In a longer-term trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open label treatment phase with Lexapro 10 or 20 mg/day, were randomized to continuation of Lexapro at their same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open label phase was defined by having a decrease of the MADRS total score to $\leq$ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to $\geq$ 22, or discontinuation due to insufficient clinical response. Patients receiving continued Lexapro experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

2. Under **INDICATIONS AND USAGE**:

[The following paragraph should be inserted as the final paragraph in this subsection i.e., replacing the current final paragraph describing the experience with Celexa.]

The efficacy of Lexapro in maintaining a response, in patients with major depressive disorder who responded during an 8-week acute treatment phase while taking Lexapro and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see Clinical Efficacy Trials, under Clinical Pharmacology). Nevertheless, the physician who elects to use Lexapro for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

3. Under **DOSAGE AND ADMINISTRATION- Maintenance Treatment**:

[The following paragraph should be inserted to replace the current language in this subsection.]

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing Lexapro 10 or 20 mg/day for periods of up to 36 weeks in patients with major depressive disorder who responded while taking Lexapro during an 8-week acute treatment phase demonstrated a benefit of such maintenance treatment (see Clinical Efficacy Trials, under Clinical Pharmacology). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

The final printed labeling (FPL) must be identical to the labeling agreed to above (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDAs 21-323/S-001 & 21-440." Approval of these submissions by FDA is not required before the labeling is used.

Pediatrics

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

Promotional Materials

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Other

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-323 for this drug product, not to this NDA 21-440. In the future, do not make submissions to NDA 21-440 except for the final printed labeling requested above.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

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