CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-365

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-365

Forest Laboratories, Inc.
Attention: John A. Baiano, Ph.D.
Assistant Director, Regulatory Affairs
Harborside Financial Center
Plaza 3, Suite 602
Jersey City, NJ 07311

Dear Dr. Baiano:

Please refer to your new drug application (NDA) dated November 2, 2001, received November 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) 5 mg/5 ml Oral Solution.

We acknowledge receipt of your submission dated October 2, 2002. Your submission of October 2, 2002 constituted a complete response to our September 5, 2002 action letter.

This new drug application provides for a new oral solution formulation of your approved oral tablet formulation of Lexapro.

We have completed the review of this application, 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 enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

We note your agreement to the labeling attached to our action letter dated September 5, 2002. For completeness, we are again attaching the final labeling to this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (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 NDA 21-365." Approval of this submission by FDA is not required before the labeling is used.

Please note that we have approved an expiration date of 24 months for this drug product.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

Please submit one market package of the drug product when it is available.

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

Attachment

APPEARS THIS WAY
ON ORIGINAL

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
11/27/02 08:08:02 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-365

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-365

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 application (NDA) dated November 2, 2001, received November 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) 5 mg/5 ml Oral Solution.

We acknowledge receipt of your following submissions dated: February 28, June 27, and August 1, 2002. We also refer to your submission dated August 19, 2002. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application provides for a new oral solution formulation of your approved oral tablet formulation of Lexapro.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Clinical – Labeling

Accompanying this letter (Attachment) is the Agency's labeling of Lexapro solution in the treatment of major depressive disorder (MDD). We have used, as our base labeling, the labeling approved in Agency letters dated August 14, 2002 (NDA 21-323) and August 29, 2002 (NDA 21-440). The changes in the labeling pertaining to the oral solution are identical to those proposed in your November 2, 2001 submission.

Chemistry, Manufacturing, and Controls

1. Please provide a list of the equipment (i.e., equipment type and manufacturer) used to manufacture, package and label Lexapro (escitalopram oxalate) 5 mg/5 mL Oral Solution.
2. Please provide the certificate of analyses (COAs) for the following batches of escitalopram oral solution: Lot numbers 00906, 01001, 00601, 00604 and 00605.
3. Please include, as part of the regulatory release specifications, a chiral assay for determining the enantiomeric

purity of Lexapro (escitalopram oxalate) 5 mg/5 mL Oral Solution. Please provide the FDA with a copy of the regulatory release chiral test method and the validation results, which demonstrates the methods suitability for its intended use.

4. Please provide the LOD/LOQ for the identified degradation products [redacted] when analyzed for by the HPLC method [redacted]

5. Please provide a description (e.g., lot number, manufacturer) of [redacted] reference materials, which are used by Forest Laboratories to perform release testing of Lexapro (escitalopram oxalate) 5 mg/5 mL Oral Solution.

6. Please correct Tables 2-2 and/or Table 2-3 in Section 4.5.11 of NDA 21-365 to correctly describe the Packaging Configuration used for drug product stability samples.

7. Based on the available stability data the Agency recommends lowering the proposed specifications for the impurities [redacted] respectively. These specifications are identical to the currently approved specifications for these impurities in the product Celexa (citalopram HBr) 10 mg/5 mL Oral Solution (NDA 21-046).

8. Please provide a copy of the chiral normal phase HPLC method used to evaluate the enantiomeric purity of escitalopram oxalate oral solution 5 mg/5 mL and 10 mg/5 mL stability samples. Please include data (e.g., chromatograms), which validates this chiral normal phase HPLC method for its intended use.

9. The Agency notes Forest's decision [redacted] Please commit to testing the primary stability samples for enantiomeric purity for the proposed expiry date (i.e., 24 months). Please note that data supporting enantiomeric purity of the drug product is expected for the full expiry period.

10. Please provide the development history which led to the proposed commercial formulation for Lexapro (escitalopram oxalate) 5 mg/5 mL Oral Solution.

11. Please provide the exact categorical exclusion (i.e., 21 CFR reference) that is claimed by Forest Laboratories, Inc for the manufacture of Lexapro (escitalopram oxalate) 5 mg/5 mL Oral Solution. Please state whether, to the applicant's knowledge, any extraordinary circumstances exist (21 CFR 25.15(d)) concerning the manufacture of Lexapro (escitalopram oxalate) 5 mg/5 mL Oral Solution.

Microbiology

A preservative effectiveness test needs to be conducted to determine the effect of the preserved drug product on microorganisms. One of the primary stability batches should be tested for preservative effectiveness at the proposed shelf life of the product.

We note that the results of the antimicrobial effectiveness testing have been submitted in a submission dated August 19, 2002. As stated previously in this letter, this submission will be reviewed in the next review cycle.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

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, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Attachment

APPEARS THIS WAY
ON ORIGINAL