CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-365

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-365 _____ _____

Drug Lexapro (escitalopram) 5 mg/5 ml Oral Solution Applicant Forest

RPM Paul David Phone x4-5530

■505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s) 58,380

Application classifications:

Chem Class 2020100
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:

Primary 9-5-02
Secondary 9-5-02

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐User Fee Exemption

- Action Letter..... ☐AP ■AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... X
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... N/A
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No
  Immediate container and carton labels ..... N/A
  Nomenclature review ..... N/A

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.

  Exception for review (Center Director's memo)..... N/A
  OC Clearance for approval..... N/A

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ■ Materials requested in AP letter
- Post-marketing Commitments N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- Was Press Office notified of action (for approval action only)?..... ☐ Yes ■ No
  - Copy of Press Release or Talk Paper.....
- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- Exclusivity Summary X
- Debarment Statement X
- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located .....
- Correspondence/Memoranda/Faxes X
- Minutes of Meetings X
  - Date of EOP2 Meeting None
  - Date of pre NDA Meeting 11-14-00
  - Date of pre-AP Safety Conference N/A
- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X
- Clinical review(s) and memoranda X
- Safety Update review(s) ..... N/A
- Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  - Pediatric Page..... X
  - ☐ Pediatric Exclusivity requested? ☐ Denied ■Granted ■Not Applicable 7-15-02

- ♦ Statistical review(s) and memoranda ..... N/A
- ♦ Biopharmaceutical review(s) and memoranda..... X
- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....
- ♦ Microbiology (efficacy) review(s) and memoranda X
- ♦ DSI Audits X
  ☐Clinical studies ■ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ CMC review(s) and memoranda X
- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ♦ DMF review(s) X
- ♦ Environmental Assessment review/FONSI/Categorical exemption X
- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ♦ Facilities Inspection (include EES report) N/A
  Date completed 5-10-02 ..... ■Acceptable ☐Not Acceptable
- ♦ Methods Validation ..... ☐ Completed ■ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ Pharm/Tox review(s) and memoranda X
- ♦ Memo from DSI regarding GLP inspection (if any) ..... N/A
- ♦ Statistical review(s) of carcinogenicity studies ..... N/A
- ♦ CAC/ECAC report ..... N/A

David

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 1, 2002

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV July 01, 02
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-365
Escitalopram® Oral Solution (S-citalopram; Lu 26-054)
Sponsored by Forest Laboratories Inc., New York, NY

TO: Russell G. Katz, M.D.
Director,
Division of Neuropharmacological
Drug Products (HFD-120)

At the request of HFD-120, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Protocol #: SCT-PK-06
Title: "A Single-Dose, Open Label, Randomized, Two-Way Crossover, Bioequivalence Study Comparing Lu 26-054 Tablets (20 mg) with Lu 26-054 Oral Solution (20 mg) in Human Volunteers"

The clinical and analytical portions of the study were conducted at _____ and at Forest Laboratories, Farmingdale, NY, respectively.

At the conclusion of the inspection at _____ (5/28-6/4/02), no Form 483 was issued. Following the inspection at Forest Laboratories (3/26-28/02), Form 483 was issued. The significant inspectional findings and an evaluation of them follows:

Clinical Site: ---

1. QTc values in the electrocardiograms (ECG) did not match with the values reported in the study.

The sponsor did not report the QTc values on the ECG printouts (Exhibit 1). Instead, the sponsor substituted QTc values using the Bazett's correction [$QTc = QT/\sqrt{60/HR}$] (Exhibit 2). The biopharmaceutics reviewer needs to evaluate the significance of this finding.

Analytical Site: **Forest Laboratories, Farmingdale, NY.**

2. Failure to submit stability data of S-citalopram (in solution and human plasma).

Only stability of the racemic compound was reported in the NDA submission. The inspection revealed that Forest also had stability data of the S-enantiomer in human plasma and in solution. This information, however, was NOT reported. Nonetheless, a review of the stability data during the inspection revealed that S-citalopram was stable for the storage period of the study samples.

In their response, the firm stated that, in future, they will include all relevant stability data in the NDA submission. Also, they will include the S-citalopram stability reports in next update of NDA 21-365 (scheduled for June 2002).

3. Failure to investigate and resolve the shifting of retention times for S-citalopram and its metabolite chromatographic peaks in 7 out of 10 runs.

The shift in the retention times of the analytes was not investigated. This finding does not invalidate the results.

4. The SOP PKS-001 (version 3) for reassay of biological samples failed to exclude the subjective criterion of selecting outliers based on study personnel's discretion.

The study personnel's discretion introduces possible bias. Forest responded that they will revise their SOP to exclude reassay of samples based on study personnel's discretion.

5. **Failure to follow SOP in that the freezer used to store study samples was calibrated only once, instead of twice, between 7/00 and 6/01.**

   The freezer temperature was within specified limits during study sample storage (8/00- 10/00) and the calibration check on 1/29/01 showed that the freezer temperature was accurate.

The Items 2 to 5 are not likely to affect the study results. The firm has promised to correct the objectionable practices for future studies.

Conclusions:

We recommend that the data for Study SCT-PK-06 be accepted for Agency review.

The biopharmaceutics reviewer needs to ascertain the relevance of using Bazett's correction to estimate QTc (Item 1).

Following your review, please append this to the original NDA submission.

Sriram Subramaniam, Ph.D.

Final Classifications:
NAI - ______________________________
VAI - Forest Laboratories, Farmingdale, NY.

Attachments

cc:
HFD-45 rf
HFD-345 Subramaniam(2)/cf
HFD-860 Baweja
HFD-120 David
HFR-SE2560 Menendez
HFR-NE1500 Hansen
Draft: SS 6/20/02, 7/1/02
Edited: MFS 7/1/02 MKY MKY 7/1/02
File:5409;O:\BE\EIRCOVER\21365FOR.ESC
FACTS # 272917

(E)

Number of Pages Redacted 4

❖❖❖

Confidential,
Commercial Information

(E)

F

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

F

(5)

Number of Pages Redacted 24

❖❖❖

Draft Labeling
(not releasable,

(5)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 3, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable action for NDA 21-365 for oral solution of escitalopram (5 mg/mL)

TO: File, NDA 21-365
[Note: This memo should be filed with the 11-2-01 original submission of this application.]

Lexapro (escitalopram) is currently approved for the treatment of MDD in immediate release tablet strengths of 5, 10, and 20 mg/day. This application is for an oral solution of escitalopram (5 mg/5 mL), in order to provide an alternate dosage form. It includes the results of a single dose bioequivalence study (SCT-PK-06) comparing oral solution and immediate release tablet, and also CMC information. There was no need for any additional review of this application regarding pharmacology and toxicology.

The biopharmaceutics data were reviewed by Carol Noory, Ph.D., from OCPB. She concluded that bioequivalence between the solution and the immediate release tablets had been demonstrated. It should also be noted that the site where this study was conducted was inspected by DSI and found to be acceptable.

The CMC information was reviewed by Lorenza Rocca, Ph.D. from the chemistry group, and the microbiology data were reviewed by Stephen Langille, Ph.D. Both considered the application approvable; noted deficiencies can be conveyed in the approvable letter.

This application was also reviewed by Karen Brugge, M.D., from the clinical group. Overall, she considered the application approvable, however, she did recommend that a finding of a slightly higher incidence of nausea and vomiting for the oral solution vs the tablet in normal subjects given a 20 mg dose be described in labeling. I think the difference is fairly minor, and difficult to extrapolate to patients who almost certainly would be started on lower doses than 20 mg. Consequently, I do not feel that this addition is necessary.

Conclusions and Recommendations: I agree with all reviewers that this application is approvable, with the sponsor's proposed changes to labeling.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 21-365
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA21365.01

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/

Thomas Laughren
9/3/02 09:35:05 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

(H)

Number of Pages Redacted 23

❖❖❖

Draft Labeling
(not releasable

(H)

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
Plaza 3, Suite 602
Harborside Financial Center
Jersey City, NJ 07311

Dear Dr. Baiano:

We acknowledge receipt on October 3, 2002 of your October 2, 2002 resubmission to your new drug application (NDA) for Lexapro (escitalopram oxalate) 5 mg/5 ml Oral Solution.

We consider this a complete, class 1 response to our September 5, 2002 action letter. Therefore, the user fee goal date is December 3, 2002.

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

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
10/25/02 10:47:25 AM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 21, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approval action for NDA 21-365 for oral solution of escitalopram (5 mg/5 mL)

TO: File, NDA 21-365
[Note: This memo should be filed with the 10-2-01 response to our 9-5-02 approvable letter.]

Lexapro (escitalopram) is currently approved for the treatment of MDD in immediate release tablet strengths of 5, 10, and 20 mg/day. This application is for an oral solution of escitalopram (5 mg/5 mL), in order to provide an alternate dosage form. It included the results of a single dose bioequivalence study (SCT-PK-06) comparing oral solution and immediate release tablet, and also CMC information. There was no need for any additional review of this application regarding pharmacology and toxicology.

We issued an approvable letter for this NDA on 9-5-02. This letter included: (1) CMC deficiencies; (2) microbiology deficiencies; and (3) labeling. The 10-2-02 response included complete responses to the CMC and microbiology deficiencies, and these have been reviewed by Lorenzo Rocco, Ph.D and Stephen Langille, Ph.D., respectively. Both reviewers have recommended final approval. The sponsor has accepted our 9-5-02 labeling proposal without any changes.

Conclusions and Recommendations: I agree that this application can now be approved, with the mutually agreed upon final labeling.

cc:
Orig NDA 21-365
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA21365.02

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/

Thomas Laughren
11/21/02 11:09:02 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

(I)

Number of Pages Redacted 2

❖❖❖

Draft Labeling
(not releasable

(I)