

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20699

Trade Name: EFFEXOR XR

Generic Name: VENLAFAXIN HYDROCHLORIDE

**Sponsor: WYETH-AYERST
LABORATORIES**

Approval Date: OCTOBER 20, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20699

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20699

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, Pennsylvania 19101-1245

OCT 20 1997

Dear Mr. Baranello:

Please refer to your New Drug Application (NDA) dated and received May 16, 1996, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine hydrochloride) extended release capsules 37.5 mg, 75 mg, 100 mg, and 150 mg.

Reference is also made to an Agency approvable letter dated May 2, 1997, and we also acknowledge receipt of your additional communications dated May 14, May 15, June 12, June 24, and September 3, 1997, providing for responses to our approvable letter.

The User Fee goal date for this application is December 13, 1997.

We have completed our 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 marked-up draft labeling (see ATTACHMENT). Accordingly, this application is approved effective on the date of this letter.

Please note that the labeling only reflects the strengths which you intend to market, i.e., the 37.5 mg, 75 mg, and 150 mg Capsules.

Labeling

The labeling accompanying this letter should be used for marketing this drug product. This final labeling is based on a series of telefacsimiles dated August 19, August 27, September 2, September 3, and September 11, 1997, between Wyeth-Ayerst and the Agency. We note your agreement to the Agency's proposed labeling in a telephone conversation dated September 11, 1997, between Mr. Kenneth Bonk of your firm and Mr. Paul David of this Agency.

Phase 4 Commitment

We remind you of your Phase 4 commitment to

Biopharmaceutics

Dissolution Specification

We note your agreement in correspondence dated May 14, 1997, to the following dissolution method and specification for all strengths of Effexor XR Capsules (37.5 mg, 75 mg, 100 mg, and 150 mg):

Time (hours)	RANGE (%Dissolved*)
2	
4	
8	
12	
20	

Manufacturing and Controls

1. **Expiration Date**

The Agency is approving an initial 24-month expiration dating period.

2. Methods Validation

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.

Please submit three copies of the introductory promotional material 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. These revisions are terms of the NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

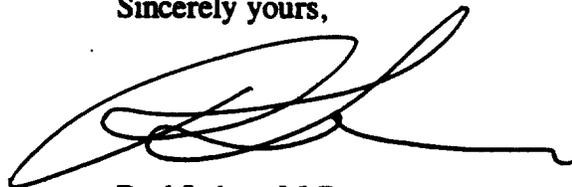
Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely yours,



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

ATTACHMENT

cc:

- Original NDA 20-699
- HFD-120/Div. File
- HFD-002/ORM
- HFD-40/DDMAC (with draft labeling)
- HFD-92/DDM-DIAB
- HFD-101/RTemple
- HFD-120/PDavid *ND 9-12-97*
- HFD-120/PLeber/TLaughren/GDubitsky *9/11/97*
- HFD-120/GFitzgerald/TSteele *9/11/97*
- HFD-120/MGuzewska/MHeimann/PDavid *9/12/97*
- HFD-222/New Drug Chemistry Division Director *9/11/97*
- HFD-613
- HFD-735/DPE
- HFD-710/TSahlroot/JChoudhury
- HFD-860/RBaweja *R 89-11-97*
- HFI-20/Press Office
- DISTRICT OFFICE
- HF-2/MedWatch

09/11/97

Doc #LTRFXRDP.AP1

APPROVED [WITH PHASE 4 COMMITMENTS]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

APPROVABLE LETTER



NDA 20-699

MAY - 2 1997

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, Pennsylvania 19101-1245

Dear Mr. Baranello:

Please refer to your pending New Drug Application (NDA) dated and received May 16, 1996, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine HCl) Extended Release 37.5 mg, 75 mg, 100 mg, and 150 mg Capsules.

We acknowledge receipt of your submissions dated July 26, August 14 and 15, September 6, 18, 20, 24, 26, and 27, October 17, and 30, November 6, 7, 18, and 20, December 19 and 20, 1996, January 6, 26, and 27, and February 19, 1997. The User Fee goal date for this application is May 16, 1997.

We have completed our review of your application, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following items:

CLINICAL

1. Labeling

Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Effexor XR. We believe it presents a fair summary of the information available on the benefits and risks of Effexor XR.

We have proposed a number of changes to the draft labeling submitted in your original May 16, 1996 submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

Our assessment of the safety of Effexor XR is based on our review of all safety information provided in your original and subsequent submissions. This original review was based on an integrated safety database with a cutoff date of approximately August 31, 1995 and on additional serious events and deaths reported up to a cutoff date of approximately December 31, 1995. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you provide a final safety update focusing on adverse events occurring subsequent to these cutoff dates. If, as is likely, the amount of additional safety information available, either from new patients or additional visits from ongoing patients, is small relative to what we already have, the safety update can focus on identifying any important new adverse events not previously reported. Consequently, rather than completely redoing the

integrated safety summary, it may be preferable for you to submit a safety update of more limited scope, e.g., it might include a line listing of any patients meeting the following criteria and not previously reported in the original NDA: any deaths; any patients dropping out for adverse events; and any patients experiencing serious events (according to the definition used for classifying such patients in your original submission). Narrative summaries should be provided for patients who died, who had a serious event or who had an unexpected cause of drop-out. In selected cases, we may ask for copies of case report forms. The Division will be happy to discuss with you more specifically what will be needed in the safety update.

3. Regulatory Status Update

Please provide any new information on the regulatory status of Effexor XR worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for Effexor XR, if appropriate, along with English translations when needed.

4. World Literature Update

Prior to the approval of Effexor XR, we require an updated report on the world's archival literature pertaining to the safety of Effexor XR. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Effexor XR. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

5. Phase 4 Post-marketing Study

Phase 4 commitments must be clearly designated "Phase 4 Commitments."
BIOPHARMACEUTICS

Dissolution Specification

The Division of Pharmaceutical Evaluation I (Office of Clinical Pharmacology and Biopharmaceutics) requests that you agree to the following dissolution method and specification for all strengths of Effexor XR Capsules (37.5 mg, 75 mg, 100 mg, and 150 mg):

Time (hours)	RANGE (%Dissolved*)
2	
4	
8	
12	
20	

Please submit 20 copies of the printed labeling, ten of which are 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.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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 such action FDA may take action to withdraw the application.

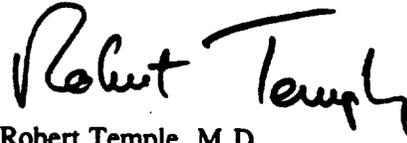
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be

approved.

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

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

Sincerely yours,

A handwritten signature in black ink that reads "Robert Temple". The signature is written in a cursive style with a large, prominent "R" and "T".

Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

ATTACHMENT

cc:

- Original NDA 20-699
- HFD-120/Div. File
- HFD-002/ORM
- HFD-92/DDM-DIAB
- HFD-120/PDavid
- HFD-120/PLeber/TLaughren/GDubitsky
- HFD-120/GFitzgerald/TSteele
- HFD-120/SBlum/MGuzewska
- HFD-710/TSahlroot/JChoudhury
- HFD-860/RBaweja/SIbrahim
- HFD-101/RTemple
- DISTRICT OFFICE
- HFD-40/DDMAC (with draft labeling)

4/8/97
3-10-97
3-20-97

7/2 3-21-97

3/14/97
3/17/97
3/13/97
3-12-97
3/12/97

ANB 3/20/97
RB 3/13/97

R Temple 5/2/97

03/07/97

Doc #LTREFFXR.AE2

APPROVABLE (AE)