Name: Effexor XR Extended-Release Capsules

Generic Name: venlafaxine hydrochloride

Sponsor: Wyeth Pharmaceuticals Inc.

Approval Date: 08/22/01

Indications: For the treatment of depression and generalized anxiety disorder.
## Reviews / Information Included in this NDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-699/S-005

APPROVAL LETTER
Dear Ms. Mann:

Please refer to your supplemental new drug application dated August 2, 2001, received August 3, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EffexorXR 37.5 mg, 75 mg, 100 mg, 150 mg.

This supplemental new drug application provides for the following change: ☐ ☑ as an alternate manufacturing site of venlafaxine hydrochloride.

We have completed the review of this supplemental application, and it is approved.

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, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the Division of Neuropharmacological Drug Products, (HFD-120)
DNDC I, Office of New Drug Chemistry 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/

Robert H. Seevers
8/22/01 09:18:28 AM
APPLICATION NUMBER:
NDA 20-699/S-005

NON-APPROVABLE LETTER(S)
Wyeth-Ayerst Laboratories  
Attention: Karel F. Bernady, Ph.D.  
Director, Marketed Products, U.S. Regulatory Affairs  
P. O. Box 8299  
Philadelphia, PA 19101-8299  

Dear Dr. Bernady:

Please refer to your supplemental new drug application dated March 4, 1999, received March 5, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EffexorXR (venlafaxine HCl) Extended Release Capsules, 37.5mg, 75mg, 100mg, and 150mg.

This supplement proposes the following change(s): as an alternate manufacturing site of venlafaxine hydrochloride.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Please describe in detail the container closure system for venlafaxine HCl manufactured at  
2. Please state the retest date for venlafaxine HCl manufactured at  
3. Please inform the FDA what Wyeth-Ayerst has done to determine the cause of the unsatisfactory physical appearance test for 37.5mg Venlafaxine HCl Extended Release (ER) Capsule stability sample manufactured with drug substance made at It is noted that the physical appearance test for the 37.5mg Venlafaxine HCl ER Capsule stability sample manufactured with drug substance made at was satisfactory at 1 month (unpackaged) and 3 months (packaged) when exposed to fluorescent light.

Recently, our inspectors could not complete inspection of your manufacturing facilities for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. A satisfactory inspection will be required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options.
under 21 CFR 314.120. 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, contact Paul David, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the Division of Neuropharmacological Drug Products, (HFD-120)
DNDC I, Office of New Drug Chemistry Center for Drug Evaluation and Research

cc:
Archival NDA 20-699
HFD-120/Div. Files
HFD-120/PDavid
HFD-120/RSeevers
HFD-120/LRocca
DISTRICT OFFICE

Drafted by: LR/June 30, 1999
Initialed by:
final:
filename: 20699SC2.WPD

NOT APPROVABLE (NA)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-699/S-005

CHEMISTRY REVIEW(S)
1. ORGANIZATION: HFD-120
2. NDA Number: 20-699
3. SUPPLEMENT NUMBERS/DATES: SCM-005
   Letter date: March 4, 1999
   Stamp date: March 5, 1999
4. AMENDMENTS/REPORTS/DATES: None
5. RECEIVED BY CHEMIST: March 9, 1999

6. APPLICANT NAME & ADDRESS
   Wyeth-Ayerst Laboratories
   P. O. Box 8299
   Philadelphia, PA 19101-8299

7. NAME OF DRUG: Effexor®XR
8. NONPROPRIETARY NAME: venlafaxine hydrochloride
9. CHEMICAL NAME/STRUCTURE:
   (R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]
   cyclohexanol hydrochloride

10. DOSAGE FORM(S): Extended Release Capsules
11. POTENCY: 37.5mg, 75mg, 100mg, 150mg
12. PHARMACOLOGICAL CATEGORY: Treatment of Depression
13. HOW DISPENSED: X (Rx) (OTC)
14. RECORDS & REPORTS CURRENT: X Yes No
   REVIEW RECORDS & REPORTS CURRENT X Yes No
15. RELATED IND/NDAlDMF: NDA 20-151, DMF r: J (Type II), DMF c: J (Type II),
                             DMF 5387 (Type I)

16. SUPPLEMENT PROVIDES FOR: Alternate active pharmaceutical ingredient manufacturing site for
    Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and
    150mg.

17. COMMENTS:
    NDA 20-699 Supplement SCM-005 (March 4, 1999) was submitted in accordance with 21 CFR
    314.70(b) which refers to supplements requiring FDA approval before the change is made. The
    supplemental application provides for C as an alternate manufacturing site of the Active
    Pharmaceutical Ingredient (API), venlafaxine HCl. The API manufactured at C will be used to
    manufacture Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg,
    100mg, and 150mg. The current approved source of the API for Effexor®XR is C and C are
    members of the same corporate entity. The API synthesis route is the same at both manufacturing
    sites.

    DMF #C J describes the manufacture of API by C
    C C DMF #C J describes manufacture of API at C
    C C DMF #C J amends to DMF #C J, submitted October 10, 1997, deals specifically with authorization to
    manufacture venlafaxine HCl at C. DMF #C J Chemistry Review No. 1 (April 30 1999)
    found the April 10, 1997 amendment to DMF #C J, adequate to support manufacture of venlafaxine
    HCl at C.
Site inspection was requested on March 19, 1999 for the API manufacturer ( ), and the drug substance release tester (Wyeth-Ayerst Laboratories, Rouses Point, NY). The Office of Compliance (OC) found the drug substance release tester acceptable (March 22, 1999). OC withheld their recommendation for the API manufacturer (March 31, 1999) for the reason "Firm Not Ready" for inspection. On June 22, 1999, a second inspection request was submitted to OC. As of June 29, 1999, has not received an acceptable review status for the manufacture of API at . The current EER Detail Report is appended to this review.

18. CONCLUSIONS & RECOMMENDATIONS:
Not Approvable. On March 19, 1999 this reviewer requested that facility be inspected for conformance with good manufacturing practices (CGMP). On March 31, 1999 the Office of Compliance withheld their decision because the firm was not ready for inspection. A satisfactory inspection will be required before this application may be approved. In addition, the following deficiencies are noted. A draft of the deficiency letter is appended to this review. Please address the following deficiencies:
- Please describe in detail the container closure system for venlafaxine HCl manufactured at and .
- Please state the retest date for venlafaxine HCl manufactured at and .
- Please inform the FDA what Wyeth-Ayerst has done to determine the cause of the unsatisfactory physical appearance test for the 37.5mg Venlafaxine HCl Extended Release (ER) Capsule stability sample manufactured with drug substance made at . It is noted that the physical appearance test for the 37.5mg Venlafaxine HCl ER Capsule stability sample manufactured with drug substance made at was satisfactory at 1 month (unpackaged) and 3 months (packaged) when exposed to fluorescent light.

REVIEWER NAME SIGNATURE DATE COMPLETED
Lorenzo A. Rocca Lorenzo Rocca 6/30/99

20. TEAM LEADER NAME SIGNATURE DATE COMPLETED
Robert H. Seevers 6/30/99

cc:
NDA 20-699/SCM005
HFD-120/Division File
HFD-120/RSeevers
HFD-120/LRocca
HFD-120/PDavid
F/T by: LRocca, File: C:\LR\Supplement\n20699\Scm-005Review.com
Appendix to Chemistry Review

NDA 20-699 Supplement SCM-005

I. Establishment Evaluation Report (EER)

29-JUN-1999

ESTABLISHMENT EVALUATION REQUEST

Application: NDA 20699/005
Stamp: 05-MAR-1999
Regulatory Due: 05-JUL-1999
Applicant: WYETH AYERST LABS
8299
PHILADELPHIA, PA 191018299
Priority: 38
Org Code: 120

Establishment Evaluation Report (EER)

Application Comment: THE ACTIVE PHARM INGREDIENT (API) WILL BE OBTAINED FROM THE FOLLOWING SOURCES: 1) API WILL BE TESTED BY EITHER ☐ OR WYETH-AYERST LABS ROUSES POINT, NY AND RELEASED AT WYETH-AYERST LABS ROUSES POINT, NY (DMF5387) (on 18-MAR-1999 by L. ROCCA (HFD-810) 301-594-2562)

FDA Contacts: P. DAVID (HFD-120) 301-594-2850, Project Manager
L. ROCCA (HFD-810) 301-594-2562 , Review Chemist
R. SEEVERS (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation: WITHHOLD on 31-MAR-1999 by J. DAMROGIO (HFD-324) 301-827-0062

Establishment: 1310337

WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979

DMF No: 5387

Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CTL
GAI Status: GAI ALERT

Establishment Comment:

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Establishment: 1210337

WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979

DMF No: 5387

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CTL
GAI Status: NONE

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Milestone Comment:

WITHHOLD on 31-MAR-1999 by J. DAMROGIO (HFD-324) 301-827-0062

Establishment: 1310337

WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979

DMF No: 5387

Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CTL
GAI Status: GAI ALERT

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Milestone Comment:

ACCEPTABLE BASED ON PROFILE

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DAMROGIOJ

RCCAL

DAMROGIOJ

RCCAL

DAMROGIOJ
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of trade secret and/or confidential commercial information from Chemistry Review #1
CHEMIST REVIEW 2
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
2. NDA Number: 20-699
3. SUPPLEMENT NUMBERS/DATES: SCM-005 (BC)
   Letter date: June 19, 2000
   Stamp date: June 20, 2000
4. AMENDMENTS/REPORTS/DATES: None
5. RECEIVED BY CHEMIST: June 7, 2000

6. APPLICANT NAME & ADDRESS
   Wyeth-Ayerst Laboratories
   P. O. Box 8299
   Philadelphia, PA 19101-8299

7. NAME OF DRUG: Effexor\textsuperscript{\textregistered}XR
8. NONPROPRIETARY NAME: venlafaxine hydrochloride
9. CHEMICAL NAME/STRUCTURE:
   \[
   (R/S)-1-([2\text{-dimethylamino})\text{-}1\text{-}(4\text{-methoxyphenyl})\text{ethyl}]
   \text{cyclohexanol hydrochloride}
   \]

10. DOSAGE FORM(S): Extended Release Capsules
11. POTENCY: 37.5mg, 75mg, 100mg, 150mg
12. PHARMACOLOGICAL CATEGORY: Treatment of Depression
13. HOW DISPENSED: X (Rx) (OTC)
14. RECORDS & REPORTS CURRENT: X Yes No
   REVIEW RECORDS & REPORTS CURRENT Yes X No
15. RELATED IND/NDA/DMF: NDA 20-151, DMF \( \subseteq \) (Type II), DMF \( \subseteq \) \( \subseteq \) (Type II),
    DMF 5387 (Type I)
16. SUPPLEMENT PROVIDES FOR: Alternate active pharmaceutical ingredient manufacturing site for
    Effexor\textsuperscript{\textregistered}XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and
    150mg.
17. COMMENTS:
   NDA 20-699 Supplement SCM-005 (March 4, 1999) was submitted in accordance with 21 CFR
   314.70(b) which refers to supplements requiring FDA approval before the changes are made. The
   supplemental application provides for \( \subseteq \) facility as an alternate
   manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl. The API
   manufactured at \( \subseteq \) \( \subseteq \) will be used to manufacture Effexor\textsuperscript{\textregistered}XR (venlafaxine hydrochloride)
   Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg. The current approved source of the
   API for Effexor\textsuperscript{\textregistered}XR is \( \subseteq \) \( \subseteq \) and \( \subseteq \) \( \subseteq \) are members of the same corporate entity. The API synthesis route is the same at both manufacturing
   sites.

   DMF \( \subseteq \) \( \subseteq \) describes the manufacture of API by \( \subseteq \)
   \( \subseteq \) DMF \( \subseteq \) \( \subseteq \) describes manufacture of API at \( \subseteq \)
   The amendment to DMF \( \subseteq \) \( \subseteq \), submitted October 10, 1997, deals specifically with authorization to
   manufacture venlafaxine HCl at \( \subseteq \) \( \subseteq \) \( \subseteq \) DMF \( \subseteq \) \( \subseteq \) Chemistry Review No. 1 (April 30 1999)
found the April 10, 1997 amendment to DMF adequate to support manufacture of venlafaxine HCl at C

Site inspection was requested on March 19, 1999 for the API manufacturer (C), and the drug substance release tester (Wyeth-Ayerst Laboratories, Rouses Point, NY). The Office of Compliance (OC) found the drug substance release tester acceptable (March 22, 1999). OC withheld their recommendation for the API manufacturer (March 31, 1999) for the reason "Firm Not Ready" for inspection. On June 22, 1999, a second inspection request was submitted to OC. OC withheld their recommendation for the API manufacturer (July 28, 1999) for the reason "Firm Not Ready" for inspection. OC’s recommendation was updated on March 24, 2000 following a cGMP inspection of the C on C. The OC withheld their recommendation for the API manufacture due to "Inadequate QA Functions". On July 12, 2000, a third inspection request was submitted to OC following receipt of supplemental amendment SCM-005 (BC). OC withheld their recommendation for the API manufacturer (July 28, 2000) with the comment, "Firm continues to not be acceptable". In addition, OC has noted that the C facility is under consideration for a warning letter. The current EER Detail Report is appended to this review.

At the time supplemental amendment SCM-005 was initially reviewed (see NDA20-699/SCM-005 Chemistry Review 1, June 30, 1999) three deficiency questions were submitted to the sponsor. In the current supplemental amendment SCM-005(BC), Wyeth-Ayerst has responded to each question. The sponsor’s responses are satisfactory and are summarized in the Review Notes section.

18. CONCLUSIONS & RECOMMENDATIONS:
Not Approvable. On July 12, 2000, this reviewer requested that the C facility be inspected for conformance with good manufacturing practices (cGMP). On July 28, 2000 the Office of Compliance withheld their decision because the firm continues to not be acceptable, at the same time the OC has noted that reinspection of the facility will be needed to determine adequate and acceptable corrective action. The sponsor has provided satisfactory responses to the deficiency questions raised when supplemental amendment SCM-005 was initially reviewed (see NDA20-699/SCM-005 Chemistry Review 1, June 30, 1999).

19. REVIEWER NAME SIGNATURE DATE COMPLETED

Lorenzo A. Rocca

20. TEAM LEADER NAME SIGNATURE DATE COMPLETED

Robert H. Seevers
Redacted _____ page(s)
of trade secret and/or
confidential commercial
information from

Chemistry Review # 2
Appendix to Chemistry Review

NDA 20-699 Supplement SCM-005 (BC)

C. Establishment Evaluation Report (EER)

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Application Comment: THE ACTIVE PHARM INGRDIENT (API) WILL BE OBTAINED FROM THE FOLLOWING SOURCES: 1) API WILL BE TESTED BY EITHER 2) OR WYETH-AYERST LABS ROUSES POINT, NY AND RELEASED AT WYETH-AYERST LABS ROUSES POINT, NY (DMF5387) (on 18-MAR-1999 by L. ROCCA (HFD-810) 301-594-5357)

FDA Contacts: P. DAVID (HFD-120) 301-594-2850, Project Manager
L. ROCCA (HFD-810) 301-594-5357, Review Chemist
R. SEEVERS (HFD-120) 301-594-2850, Team Leader

Overall Recommendation: WITHHOLD on 31-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 28-JUL-2000 by P. ALCOCK (HFD-324) 301-827-0062
WITHHOLD on 27-MAR-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: [ ]

DMF No: [ ]

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: POTENTIAL OAI

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<td>18-JUL-2000</td>
<td>DO RECOMMENDATION</td>
<td>OC RECOMMENDATION</td>
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The 12/99 EI is still under consideration for a WARNING LETTER and, as yet, the firm’s written response is PARTIAL.

Establishment: 1310337
WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979

DMF No: 5387
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CTL
OAI Status: NONE

<table>
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<th>Milestone Name</th>
<th>Date</th>
<th>Decision &amp; Reason Creator</th>
<th>Milestone Comment</th>
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<tr>
<td>SUBMITTED TO OC</td>
<td>19-MAR-1999</td>
<td>ACCEPTABLE</td>
<td>PROFILE</td>
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<td>OC RECOMMENDATION</td>
<td>22-MAR-1999</td>
<td>DMBROGIOJ</td>
<td>REASONS</td>
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CHEMIST REVIEW 3
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
2. NDA Number: 20-699
3. SUPPLEMENT NUMBERS/DATES: SCM-005 (AC)
   Letter date: August 2, 2001
   Stamp date: August 3, 2001
4. AMENDMENTS/REPORTS/DATES: None
5. RECEIVED BY CHEMIST: August 20, 2001

6. APPLICANT NAME & ADDRESS
Wyeth-Ayerst Laboratories
P. O. Box 8299
Philadelphia, PA 19101-8299

7. NAME OF DRUG:
Effexor®XR

8. NONPROPRIETARY NAME:
venlafaxine hydrochloride

9. CHEMICAL NAME/STRUCTURE:
(R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]
cyclohexanol hydrochloride

10. DOSAGE FORM(S):
Extended Release Capsules

11. POTENCY:
37.5mg, 75mg, 100mg, 150mg

12. PHARMACOLOGICAL CATEGORY:
Treatment of Depression

13. HOW DISPENSED:
   X (Rx) (OTC)

14. RECORDS & REPORTS CURRENT:
   REVIEW RECORDS & REPORTS CURRENT
   X Yes No

15. RELATED IND/NDA/DMF:
NDA 20-151, DMF ☑ (Type II), DMF ☑ (Type II),
DMF 5387 (Type I)

16. SUPPLEMENT PROVIDES FOR: Alternate active pharmaceutical ingredient manufacturing site for Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg.

17. COMMENTS:
NDA 20-699 Supplement SCM-005 (March 4, 1999) was submitted in accordance with 21 CFR 314.70(b) which refers to supplements requiring FDA approval before the changes are made. The supplemental application provides for ☑ facility as an alternate manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl. The API manufactured at ☑ will be used to manufacture Effexor®XR (venlafaxine hydrochloride) Extended Release Capsules 37.5mg, 75mg, 100mg, and 150mg. The current approved source of the API for Effexor®XR is ☑ and ☑ are members of the same corporate entity. The API synthesis route is the same at both manufacturing sites.

Site inspection was requested on March 19, 1999 for the API manufacturer ( ☑ ☑ ☑ ), and the drug substance release tester (Wyeth-Ayerst Laboratories, Rouses Point, NY). The Office of Compliance (OC) found the drug substance release tester acceptable (March 22, 1999). OC withheld their recommendation for the API manufacturer (March 31, 1999) for the reason “Firm Not Ready” for inspection. On June 22, 1999, a second inspection request was submitted to OC. OC
withheld their recommendation for the API manufacturer (July 28, 1999) for the reason "Firm Not Ready" for inspection. OC's recommendation was updated on March 24, 2000 following a cGMP inspection of the facility. The OC withheld their recommendation for the API manufacturer due to "Inadequate QA Functions". On July 12, 2000 a third inspection request was submitted to OC following receipt of supplemental amendment SCM-005 (BC). OC withheld their recommendation for the API manufacturer (July 28, 2000) with the comment, "Firm continues to not be acceptable". In addition, OC has noted that the facility is under consideration for a warning letter. On August 16, 2001 a fourth inspection request was submitted to OC following receipt of supplemental amendment SCM-005 (AC). OC found the API manufacturer acceptable (August 16, 2001).

18. CONCLUSIONS & RECOMMENDATIONS:
Recommend issuing an approval letter. On August 16, 2001 the Office of Compliance found the facility acceptable (based on profile) as an alternate manufacturing site of the Active Pharmaceutical Ingredient (API), venlafaxine HCl.

19. REVIEWER NAME            SIGNATURE            DATE COMPLETED
   Lorenzo A. Rocca

20. TEAM LEADER NAME           SIGNATURE            DATE COMPLETED
   Robert H. Seevers

cc:
NDA 20-699/SCM005(AC)
HFD-120/Division File
HFD-120/RSeevers
HFD-120/LRocca
HFD-120/Pdavid

F/T by: LRocca, File: C:\data\LR\Supplement\n20699\Scm-005Review_3.com
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Lorenzo Rocca
8/21/01 10:14:49 AM
CHEMIST

Robert H. Seevers
8/22/01 09:13:11 AM
CHEMIST
Attention: Karel F. Bernady, Ph.D., Director

Dear Dr. Bernady:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Effexor XR

NDA Number: 20-699

Supplement Number: S-005

Date of Supplement: March 4, 1999

Date of Receipt: March 5, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 4, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc:
   Original NDA 20-699/005
   HFD-120/Div. Files
   HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\20-699.005

SUPPLEMENT ACKNOWLEDGEMENT