CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-699/S-032

Name:	Effexor XR Extended-Release Capsules
Generic Name:	venlafaxine hydrochloride
Sponsor:	Wyeth Pharmaceuticals Inc.
Approval Date:	02/26/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-032

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-032

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-032

Wyeth Pharmaceuticals
Attention: Tracy D. Rockney, JD
Director, Global Brand Management
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Ms. Rockney:

Please refer to the your supplemental new drug application dated November 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine hydrochloride) Extended Release 37.5 mg, 75 mg, and 150 mg Capsules.

We additionally refer to an Agency action letter dated December 18, 2002.

We acknowledge receipt of your complete response dated January 23, 2003, to the above action letter.

The above submission, submitted as a "Prior Approval" supplemental application, provides for an Effexor XR Patient Brief Summary.

We have completed the review of this supplemental application, 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 submitted final printed labeling. Accordingly, this supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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 regarding this letter, call Mr. 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

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/s/

Russell Katz
2/26/03 07:37:08 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-032

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-699/S-032

Wyeth Pharmaceuticals
Attention: Tracy Rockney, JD
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Ms. Rockney:

Please refer to the your supplemental new drug application dated November 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor XR (venlafaxine hydrochloride) Extended Release 37.5 mg, 75 mg, and 150 mg Capsules.

The above submission, submitted as a "Prior Approval" supplemental application, provides for an Effexor XR Patient Brief Summary.

We have completed our review of this supplemental application, and it is approvable.

Before this submission can be approved, it will be necessary to make the following changes to the document:

1. This leaflet should be titled: "PATIENT INFORMATION."

2. The term "medicine" should be used in place of "medication" throughout the PPI.

3. Typical structure for a Patient Package Insert (PPI) should be followed as closely as possible for this specific product class. Here are the typical headlined sections (usually in question format, but this is not necessary):

   What is the most important information that I should know about Effexor XR?
   What is Effexor XR?
   Who should not take Effexor XR?
   How should I take Effexor XR?
   What should I avoid while taking Effexor XR?
   What are the possible side effects of Effexor XR?
   General advice about Effexor XR
   Ingredients and storage information

4. The first headlined section after the introductory paragraph should be "What is the most important information I should know about Effexor XR?" This section should contain the contraindication/warning regarding use with a monoamine oxidase inhibitor (MAOI) including the details about not using Effexor XR within 14 days of using a MAOI. This does not need to be repeated elsewhere. For example, the MAOI information in the section entitled "Effexor XR is not for everyone" (usually referred to as "Who should not take Effexor XR?")

should be moved up to "What is the most important information I should know about Effexor XR?" (The allergy information can stay in the section "Who should not take Effexor XR?" and should refer the reader to a list of the inactive ingredients that should be included at the end of the leaflet.)

5. The section "How Effexor XR works" is misleading and promotional. The second sentence in this section must be deleted. However, there is a mechanism of action for Effexor XR given in the prescriber labeling, so it cannot state that it is [ ] Here is some suggested wording for this section:

   Effexor XR is thought to work by affecting two naturally occurring brain chemicals, serotonin and norepinephrine. This helps relieve your symptoms. It may take several weeks for your symptoms to get better with Effexor XR.

6. The section "What to tell your doctor before taking Effexor XR" is usually not a separate section. This information is found under the header "Who should not take Effexor XR?" Here is suggested wording for this part:

   Do not take Effexor XR if

   you are allergic to Effexor XR or any of its ingredients. The inactive ingredients are listed at the end of this leaflet.

   Effexor XR can make some conditions worse. Tell your doctor about all your medical problems. ***Be sure to tell your doctor if you have or had***

   - *suicidal thoughts*
   - *high blood pressure. Effexor XR can increase your blood pressure.*
   - *heart disease. Effexor XR can increase your heart rate (pulse).*
   - *liver or kidney problems. Your dose of Effexor XR may need to be different.*
   - *symptoms of mania or hypomania, such as persistently elevated or irritable mood, a decreased need for sleep, racing thoughts, hyperactivity, and rapid, excessive speech .*
   - *glaucoma. Effexor XR may increase your eye pressure. You may need more frequent eye exams to detect an increase in eye pressure.*
   - *seizures.*

   Tell your doctor about all medicines that you plan to take, including prescription and non-prescription medicines and supplements. Your doctor will decide of you can take Effexor XR with other medicines.

   Effexor XR is not recommended for weight loss alone or in combination with phentermine or other products.

7. Delete the section entitled [ ] It is covered in other sections.

8. Delete the section entitled [ ] This information is included in "Who should not take Effexor XR?" and in "What happens when I stop taking Effexor XR?".

check your serum cholesterol periodically.

17. The paragraph beginning [ ] should be deleted, as it is now included in the section "What should I avoid while taking EFFEXOR XR?"

18. Delete the section "How long should I use Effexor XR?"

19. In the section entitled "What happens when I stop using Effexor XR (a necessary section in this label because of the special circumstance of discontinuation syndrome), the first sentence should be revised to be specific for Effexor XR (i.e., replace [ ] with "Effexor XR"). Following this sentence, the discontinuation symptoms should appear as a bulleted list. The paragraph is too complex for the lay public and should be simplified. Suggested wording is below:

    When people suddenly stop using Effexor XR, they can get symptoms from stopping the medicine too fast. Some of these symptoms include

    - *agitation*
    - *anxiety*
    - *confusion*
    - *diarrhea*
    - *dizziness or vertigo*
    - *dry mouth*
    - *fasiculation*
    - *headaches*
    - *hypomania*
    - *impaired coordination*
    - *insomnia*
    - *loss of appetite*
    - *nausea*
    - *nervousness*
    - *nightmares*
    - *sensory disturbances (including electric shock sensations)*
    - *somnolence*
    - *sweating*
    - *tiredness*
    - *tremor*
    - *unpleasant mood*
    - *vomiting*

    Do not stop taking Effexor XR without talking with your doctor first. Your doctor may want to slowly decrease your dose of Effexor XR to avoid these kinds of symptoms.

20. The section entitled "What to do for an overdose" is unnecessary. This information may de deleted or moved to "How should I take Effexor XR?"

21. A section entitled [ ] should be added. This section should read

[ ] *the most important information about Effexor XR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Effexor XR that is written for health professionals.*

22. Add a section entitled "What are the ingredients in Effexor XR?" and list the active and all of the inactive ingredients.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

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

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

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/s/

Russell Katz
12/18/02 10:15:17 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-032

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 20-699

Sponsor:	Wyeth
Drug:	Effexor XR
Indication:	Depression and GAD
Material Submitted:	Patient Brief Summary (SLR-032)
Correspondence Date:	November 21, 2002
Date Received:	November 22, 2002

I. Background

The sponsor has submitted a proposed three-page Patient Brief Summary for Effexor XR. This document is intended to provide a summary of information related to side effects, contraindications, benefits, and risks of Effexor XR in patient-friendly language.

I have reviewed this document, using Effexor XR labeling for reference, and provided comments below.

II. Comments on the Patient Brief Summary

Page 2: The listing of the most common side effects at the bottom of the page contains the event "Confusion/agitation [ ]." The phrase in parentheses contradicts the [ ] section of labeling, which indicates that there were no overall differences in safety between [ ] patients. I am not aware of any clinical data suggesting that the risk of confusion and agitation associated with Effexor XR is higher in [ ] patients. This parenthetic phrase should be removed.

Page 3: The first bullet at the top of the page mentions [ ] as a possible side effect of Effexor XR. This is too non-specific to be helpful and will have no meaning to patients. It should be removed.

Page 3: The second bullet mentions the possibility of [ ] It

would be helpful for the patient to understand the clinical significance of [ ]. Also, the term [ ] [ ] may not be familiar to many patients and could be replaced by the term [ ] The following is suggested to replace the proposed statement:

[ ]

Page 3: The possibility of mania or hypomania should be added as a bullet at the top of the page, such as:

> *Symptoms of mania such as persistently elevated or irritable mood, a decreased need for sleep, racing thoughts, hyperactivity, and rapid, excessive speech.*

Page 3: The first full paragraph states that Effexor XR may cause an increase in cholesterol [ ] [ ] I am not aware of any clinical data regarding the relative increases in cholesterol [ ] associated with Effexor XR although it does seem that this agent does increase total cholesterol. The second sentence, which discusses these [ ], should be removed.

Page 3: This summary does not specifically mention the possibility of [ ] with Effexor XR. The following should be added as the second full paragraph on this page:

> [ ] *eye pressure.* [ ]
>
> [ ]
>
> *sudden, unexpected eye pain, eye redness, or* [ ]
> *changes in your vision,* [ ]
> [ ]

Page 3: Under the section entitled "What happens when I stop taking Effexor XR," the listing of possible symptoms associated with the discontinuation of Effexor XR is rather vague (e.g., [ ]). It is

suggested that this list be replaced with the list of more specific adverse events in Effexor XR labeling.

III. Conclusions and Recommendations

It is recommended that the above comments be communicated to the sponsor. This supplement may be approved contingent on the sponsor adequately addressing the above concerns.

Gregory M. Dubitsky, M.D.
December 10, 2002

cc: NDA 20-699
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PDavid

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/s/

Greg Dubitsky
12/10/02 02:07:34 PM
MEDICAL OFFICER

Thomas Laughren
12/11/02 08:00:56 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA 20-699

Sponsor:	Wyeth
Drug:	Effexor XR
Indication:	Depression and GAD
Material Submitted:	Revised Patient Brief Summary (SLR-032)
Correspondence Date:	January 23, 2003
Date Received:	January 24, 2003

I. Background

On November 21, 2002, Wyeth submitted a proposed three-page Patient Brief Summary for Effexor XR. This document is intended to provide a summary of information related to the side effects, contraindications, benefits, and risks of Effexor XR in patient-friendly language.

This document was reviewed by the undersigned as well as by Lisa Stockbridge from the Division of Drug Marketing, Advertising, and Communications (DDMAC).[1] Comments from both reviews were communicated to Wyeth in a 12-18-02 approvable letter from the Division (Tab D of the current submission).

This submission contains Wyeth's response to our letter and includes a revised Patient Brief Summary (Tab A).

II. Comments on the Revised Patient Brief Summary

I examined this document and it satisfactorily incorporates the changes we had requested in our approvable letter.

However, there are some further revisions that the sponsor now proposes to implement. These are listed by section below.

[1] See my Review and Evaluation of Clinical Data dated 12-10-02 and a DDMAC Memorandum dated 12-12-02.

Who should not take EFFEXOR XR?

The generic name (venlafaxine HCl) is added in parentheses to the warning about allergies.

The term "thyroid problems" has been added to the list of conditions of which patients should advise their doctors.

Patients are advised to inform their doctors of natural and herbal supplements they are taking.

What are the possible side effects of EFFEXOR XR?

The term [ ] has been changed to "abnormal ejaculation" for better consistency with terminology in labeling.

The preface to the listing of possible side effects is qualified by the word "included" to indicate that this list does not encompass every common side effect found in labeling.

The side effect "loss of appetite" has been removed from the listing of common side effects. The sponsor proposes to delete this side effect because they are concerned that it may lead some patients to use Effexor XR to facilitate weight loss. It is noted that the related term [ ] is included in the list of common side effects.

Tell your doctor right away if you have

Examples of specific manic symptoms are added to further define "symptoms of mania or hypomania" for the reader.

What happens when I stop using EFFEXOR XR?

Layperson's terminology has been added in parentheses to the terms fasciculation (muscle twitching), insomnia (trouble sleeping), and somnolence (sleepiness). It is noted that the term "fasciculation" is misspelled as "fasiculation" in the Summary.

The statement concerning a slow decrease in dose to address discontinuation symptoms has been qualified by adding the word "help" (slowly decrease your dose of EFFEXOR XR to help avoid these kinds of symptoms). This communicates

that not every patient will be able to totally avoid these symptoms.

III. Conclusions and Recommendations

The revised Patient Brief Summary is acceptable from a clinical perspective. However, the sponsor should be advised that the term "fasciculation" is misspelled on the third page of the Summary.

It is recommended that this supplement be approved.

Gregory M. Dubitsky, M.D.
February 4, 2003

cc: NDA 20-699
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PAndreason
/PDavid

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/s/

Greg Dubitsky
2/4/03 03:01:03 PM
MEDICAL OFFICER

Thomas Laughren
2/4/03 04:45:28 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-699/S-032

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

Date: September 9, 2002

To: Dr. Russell Katz
Director
Division of Neuropharmacologic Drug Products
HFD-120

From: Lisa Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications
HFD-42

Re: NDA 20-699/SLR-032
Effexor XR (venlafaxine HCl) Extended Release Capsules

Material Reviewed: November 21, 2002 proposal of Patient Information leaflet (PPI) for use as Brief Summary in direct-to-consumer (DTC) advertising

Recommendations:

- This leaflet should be titled: "PATIENT INFORMATION."
- The term "medicine" should be used in place of "medication" throughout the PPI.
- Typical structure for a PPI should be followed as closely as possible for the specific product class. Here are the typical headlined sections (usually in question format, but this is not necessary):

  What is the most important information that I should know about Effexor XR?
  What is Effexor XR?
  Who should not take Effexor XR?
  How should I take Effexor XR?
  What should I avoid while taking Effexor XR?
  What are the possible side effects of Effexor XR?
  General advice about Effexor XR
  Ingredients and storage information

- The first headlined section after the introductory paragraph should be "What is the most important information I should know about Effexor XR?" This section should contain the contraindication/warning regarding use with a monoamine oxidase inhibitor (MAOI) including the details about not using Effexor XR within 14 days of using a MAOI. This does not need to be repeated elsewhere. For example, the MAOI information in the section entitled "Effexor XR is not for everyone" (usually referred to as "Who should not take Effexor XR?") should be moved up to "What is the most important information I should know about Effexor XR?" (The allergy information can stay in the section "Who should not take Effexor XR?" and should refer the reader to a list of the inactive ingredients that should be included at the end of the leaflet.)
- The section "What is Effexor XR?" is more detailed than usual, but it is consistent with the approved Zoloft PPI.

- The section "How Effexor XR works" is misleading and promotional. The second sentence in this section must be deleted. However, there is a mechanism of action for Effexor XR given in the PI, so we can't say that it is [ ]. Here is some suggested wording for this section:

  Effexor XR is thought to work by affecting two naturally occurring brain chemicals, serotonin and norepinephrine. This helps relieve your symptoms. It may take several weeks for your symptoms to get better with Effexor XR.

- The section "What to tell your doctor before taking Effexor XR" is usually not a separate section. This information is found under the header "Who should not take Effexor XR?" Here is suggested wording for this part:

  Do not take Effexor XR if

  you are allergic to Effexor XR or any of its ingredients. The inactive ingredients are listed at the end of this leaflet.

  Effexor XR can make some conditions worse. Tell your doctor about all your medical problems. ***Be sure to tell your doctor if you have or had***

  - *suicidal thoughts*
  - *high blood pressure. Effexor XR can increase your blood pressure.*
  - *problems with heart [ ]. Effexor XR can increase your heart rate (pulse).*
  - *liver or kidney problems. Your dose of Effexor XR may need to be different.*
  - [ ]
  - [ ]
  - *glaucoma. Effexor XR can increase your eye pressure. You may need more frequent eye exams.*
  - *seizures*

  Tell your doctor about all medicines that you plan to take, including prescription and non-prescription medicines and supplements. Your doctor will decide of you can take Effexor XR with other medicines.

  Effexor XR is not recommended for weight loss alone or in combination with phentermine or other products.

- Delete the section entitled [ ]. It is covered in other sections.

- Delete the section entitled [ ]. This information is included in "Who should not take Effexor XR?" and in "What happens when I stop taking Effexor XR?"

- The section "How to take Effexor XR" would be easier to understand if the instructions were bulleted out.

- Following the section "How to take Effexor XR" (or "How should I take Effexor XR?") should be a section entitled "What should I avoid while taking Effexor XR?" This section includes information about talking to your doctor before pregnancy and breast-feeding. It also includes statements such as "Do not drive a car or use heavy machinery until you know how "Effexor XR affects you" and "Avoid drinking alcohol while taking Effexor XR."

9. The section "How to take Effexor XR" would be easier to understand if the instructions were bulleted out.

10. Following the section "How to take Effexor XR" (or "How should I take Effexor XR?") should be a section entitled "What should I avoid while taking Effexor XR?" This section includes information about talking to your doctor before pregnancy and breast-feeding. It also includes statements such as "Do not drive a car or use heavy machinery until you know how Effexor XR affects you" and "Avoid drinking alcohol while taking Effexor XR."

11. The section "Possible side effects of Effexor XR" should not begin with the phrase [ ]
This phrase minimizes the risks associated with the use of the drug.

12. The list of common side effects should also include loss of appetite, gas, tremor, abnormal vision, and yawning.

13. The listing of the most common side effects at the bottom of page 2 contains the event "Confusion/agitation [ ]." The phrase in parentheses contradicts the [ ] section of prescriber labeling, which indicates that there were no overall differences in safety between [ ] patients.
We are not aware of any clinical data suggesting that the risk of confusion and agitation associated with Effexor XR is higher in [ ] patients. This parenthetic phrase should be removed.

14. The [ ] subsection minimizes the importance of the side effects with more serious risks (i.e., precautions). This phrase should be revised to "Tell your doctor right away if you have" and an explanation should follow conditions as necessary. For example

Tell your doctor right away if you have

- *extreme confusion or seizures, which may indicate very low levels of sodium in the blood.*
- *abnormal bleeding or bruising*
- *sudden, unexpected eye pain, eye redness, or changes in vision, which may indicate increased eye pressure.*
- *symptoms of mania or hypomania.*

15. The first bullet at the top of the page 3 mentions [ ] as a possible side effect of Effexor XR. This is too non-specific to be helpful and will have no meaning to patients. It should be removed.

16. The first full paragraph on page 3 states that Effexor XR may cause an increase in cholesterol [ ] [ ] We are not aware of any clinical data regarding the relative increases in cholesterol [ ] associated with Effexor XR although it does seem that this agent does increase total cholesterol. The second sentence, which discusses these [ ], should be removed, as well as the third sentence should be deleted.
The revised paragraph should read:

Effexor XR may cause an increase in your cholesterol. Your doctor may want to do blood tests to

- The section "Possible side effects of Effexor XR" should not begin with the phrase [ ] [ ] This phrase minimizes the risks associated with the use of the drug.

- The list of common side effects should also include [ ] appetite, gas, tremor, abnormal vision, and yawning.

- Delete [ ] from the list of common side effects.

- The [ ] subsection minimizes the importance of the side effects with more serious risks (i.e., precautions). This phrase should be revised to "Tell your doctor right away if you have" and an explanation should follow conditions as necessary. For example

  Tell your doctor right away if you have

  - *extreme confusion*
  - *seizures*
  - *abnormal bleeding or bruising*
  - *sudden, unexpected eye pain, eye redness, or changes in vision. You may have increased eye pressure.*

- The paragraph regarding increase in serum cholesterol may remain in the section "Possible side effects of Effexor XR". However, the second and third sentences should be deleted. The revised paragraph should read

  Effexor XR may cause an increase in your cholesterol. Your doctor may want to do blood tests to check your serum cholesterol periodically.

- The paragraph beginning [ ] should be deleted, as it is now included in the section "What should I avoid while taking EFFEXOR XR?"

- Delete the section "How long should I use Effexor XR?"

- In the section entitled "What happens when I stop using Effexor XR (a necessary section in this label because of the special circumstance of discontinuation syndrome), the first sentence should be revised to be specific for Effexor XR (i.e., replace [ ] with "Effexor XR"). Following this sentence, the discontinuation symptoms should appear as a bulleted list. The paragraph is too complex for the lay public and should be simplified. Suggested wording is below:

  When people suddenly stop using Effexor XR, they can get symptoms from stopping the medicine too fast. Some of these symptoms include

  - *nervousness*
  - [ ] *appetite*
  - *trouble sleeping*
  - *tiredness*
  - *confusion*
  - *changes in mood*
  - *nightmares*
  - *diarrhea*
  - *dizziness*
  - *dry mouth*
  - *nausea and vomiting*

- *headaches*
- *prickly or electric shock sensations*

Do not stop taking Effexor XR without talking with your doctor first. Your doctor may want to slowly decrease your dose of Effexor XR to avoid these kinds of symptoms.

- The section entitled "What to do for an overdose" is unnecessary. This information may de deleted or moved to "How should I take Effexor XR?"

- A section entitled [ ] should be added. This section should read

[ ] *the most important information about Effexor XR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Effexor XR that is written for health professionals.*

- Add a section entitled "What are the ingredients in Effexor XR?" and list the active and all of the inactive ingredients.

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/s/

Lisa Stockbridge
12/12/02 05:39:44 PM
CSO