

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

CHEMISTRY REVIEW(S)

JAN - 6 1997

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-699

CHEM. REVIEW # 1

REVIEW DATE

05-NOV-96

SUBMISSION TYPE

DOCUMENT DATE

CDE DATE

ASSIGNED DATE

ORIGINAL

16-MAY-96

17-MAY-96

21-MAY-96

AMENDMENT .N(BC)

24-SEP-96

25-SEP-96

28-SEP-96

NAME AND ADDRESS OF APPLICANT

WYETH-AYERST Laboratories
P.O. Box 8299, Philadelphia, PA 19101

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/Number:

Chem. Type/Ther. Class:

EFFEXOR XR (Extended Release) Capsules

Venlafaxine HCl

WY-45,030

PHARMACOLOGICAL CATEGORY/INDICATION

Antidepressant

DOSAGE FORM

ER Capsules

STRENGTHS

37.5, 75, 100, and 150 mg

ROUTE OF ADMINISTRATION

Oral

DISPENSED

XXX RX

___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,

or (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,

or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol hydrochloride

C₁₇H₂₇NO₂ · 2 HCl

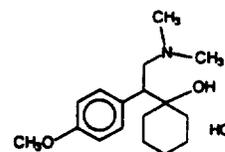
Mol. Wt:

277.41 (free base)

313.86 (HCl salt)

CAS Registry #: 99300-78-4 (HCl salt), 93413-69-5 (free base)

SUPPORTING DOCUMENTS: NDA 20-151 (EFFEXOR® Tablets),



RELATED DOCUMENTS: U.S. Patent 4,535,186 for Venlafaxine ER (issued 25-APR-96; exp. 13-DEC-2007).

CONSULTS: The EER was sent out on 30-MAY-96 (copy attached). The MV package was requested on 11-JUN-96.

REMARKS/COMMENTS: All information applicable to CM&C of venlafaxine HCl bulk drug is contained in the approved NDA 20-151 for Effexor® Tablets (immediate-release, 12.5, 25, 37.5, 50, 75, 100 mg). The extended-release formulation of venlafaxine HCl has been developed to allow for once-a-day dose administration and improved patient compliance.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-644, as amended, APPROVABLE with a 15 months' expiration dating period. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-699

HFD-120

HFD-120/MGuzewska

HF-120/PDavid/CSO

HFD-120/SBlum

HFD-810/CHOiberg (cover page only)

R/D Init by: SWE

M. Guzewska, Ph.D., Chemist

Filename: n20699.000

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-699

CHEM. REVIEW # 3

REVIEW DATE

17-MAR-97

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

ORIGINAL

16-MAY-96

17-MAY-96

AMENDMENT .N(BC)

24-SEP-96

25-SEP-96

AMENDMENT .N(BC)

30-OCT-96

31-OCT-96

NAME AND ADDRESS OF APPLICANT

WYETH-AYERST Laboratories
P.O. Box 8299, Philadelphia, PA 19101

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/Number:

Chem. Type/Ther. Class:

EFFEXOR XR (Extended Release) Capsules
Venlafaxine HCl
WY-45,030

PHARMACOLOGICAL CATEGORY/INDICATION

Antidepressant

DOSAGE FORM

ER Capsules

STRENGTHS

37.5, 75, 100, and 150 mg

ROUTE OF ADMINISTRATION

Oral

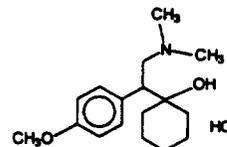
DISPENSED

RX

OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,
or (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,
or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol hydrochloride



C₁₇H₂₇NO₂ · 2 HCl

Mol. Wt: 277.41 (free base)
313.86 (HCl salt)

CAS Registry #: 99300-78-4 (HCl salt), 93413-69-5 (free base)

SUPPORTING DOCUMENTS: NDA 20-151 (EFFEXOR® Tablets),

RELATED DOCUMENTS: U.S. Patent 4,535,186 for Venlafaxine ER (issued 25-APR-96; exp. 13-DEC-2007).

CONSULTS: The evaluation of the CGMP Compliance Status of the manufacturing facilities is ongoing (copies of the EER and its current status are attached). The MV package is in preparation. The proposed trademark "EFFEXOR" is acceptable by the CDER Labeling and Nomenclature Committee. The EA information is complete and acceptable.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-699, as amended, APPROVABLE, subject to satisfactory evaluation of the manufacturing facilities. The proposed expiration dating period of 24 months at controlled room temperature (20°-25°C, 68°-77°F) is acceptable. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-699

HFD-120

HFD-120/MGuzewska

HF-120/PDavid/CSO

HFD-120/SBlum

R/D Init by: SWB


M. Guzewska, Ph.D., Chemist

Filename: n20699.003

AMB
2/20/97

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

JUL 15 1997

NDA 20-699

CHEM. REVIEW # 4

REVIEW DATE

08-JUL-97

SUBMISSION TYPE

ORIGINAL
AMENDMENT .N(BC)
AMENDMENT .N(BC)
AMENDMENT .N(BB)

DOCUMENT DATE

16-MAY-96
24-SEP-96
30-OCT-96
14-MAY-97

CDER DATE

17-MAY-96
25-SEP-96
31-OCT-96
20-MAY-97

ASSIGNED DATE

22-MAY-97

NAME AND ADDRESS OF APPLICANT

WYETH-AYERST Laboratories
P.O. Box 8299, Philadelphia, PA 19101

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/USAN:
Code Name/Number:
Chem. Type/Ther. Class:

EFFEXOR XR (Extended Release) Capsules
Venlafaxine HCl
WY-45,030

PHARMACOLOGICAL CATEGORY/INDICATION

Antidepressant

DOSAGE FORM

ER Capsules

STRENGTHS

37.5, 75, 100, and 150 mg

ROUTE OF ADMINISTRATION

Oral

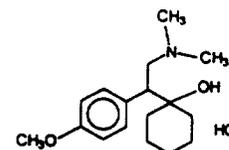
DISPENSED

~~XXX~~ RX

___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,
or (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,
or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol hydrochloride



$C_{17}H_{27}NO_2 \cdot 2 HCl$

Mol. Wt: 277.41 (free base)
313.86 (HCl salt)

CAS Registry #: 99300-78-4 (HCl salt), 93413-69-5 (free base)

SUPPORTING DOCUMENTS: NDA 20-151 (EFFEXOR® Tablets),

RELATED DOCUMENTS: U.S. Patent 4,535,186 for Venlafaxine ER (issued 25-APR-96; exp. 13-DEC-2007).

CONSULTS: The CGMP Compliance Status of the manufacturing facilities is acceptable as of 08-MAY-97. The MV package is in preparation. The proposed trademark "EFFEXOR" is acceptable by the CDER Labeling and Nomenclature Committee. The EA information is complete and acceptable.

REMARKS/COMMENTS: This submission addresses the FDA's request for revised dissolution specifications for the product capsules, as per the "approvable" letter of 02-MAY-97. Wyeth-Ayerst has agreed to the new specifications and the corresponding NDA pages have been revised. In addition, Wyeth has modified the dissolution specs for the

CONCLUSIONS & RECOMMENDATIONS: Recommend, NDA 20-699 be approved. The proposed expiration dating period of 24 months at controlled room temperature (20°-25°C, 68°-77°F) is acceptable. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-699
HFD-120
HFD-120/MGuzewska
HF-120/PDavid
FD-120/SBlum
JD Init by: SWB

M. Guzewska
7/15/97

M. Guzewska
M. Guzewska, Ph.D., Chemist

Filename: n20699.004

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

AUG - 7 1997

NDA#: 20-699

CHEMISTRY REVIEW: #15

DATE REVIEWED: 07-AUG-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	16-MAY-96	17-MAY-96	
AMENDMENT .N(BC)	24-SEP-96	25-SEP-96	
AMENDMENT .N(BC)	30-OCT-96	31-OCT-96	
AMENDMENT .N(BB)	14-MAY-97	20-MAY-97	
AMENDMENT .N(AZ)	12-JUN-97	13-JUN-97	29-JUL-97

NAME AND ADDRESS OF APPLICANT: WYETH-AYERST Laboratories
P.O. Box 8299, Philadelphia, PA 19101

DRUG PRODUCT NAME:
Proprietary: EFFEXOR®
Nonproprietary / Established / USAN: venlafaxine hydrochloride
Code Name / #: WY-40530
Chem. Type / Ther. Class: 3 S

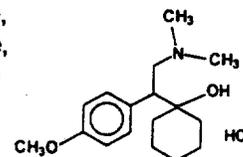
PHARMACOLOGICAL CATEGORY / INDICATION: Antidepressant
DOSAGE FORM: Extended Release Capsules
STRENGTH(S): 37.5, 75, 100 and 150 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,
or (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride,
or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol hydrochloride

C₁₇H₂₇NO₂ · 2 HCl Mol. Wt: 277.41 (free base)
313.86 (HCl salt)

CAS Registry #: 99300-78-4 (HCl salt), 93413-69-5 (free base)



SUPPORTING DOCUMENTS: Refer to MG Chemistry review No. 4 (08-JUL-97).

RELATED DOCUMENTS: Refer to MG Chemistry review No. 4 (08-JUL-97).

CONSULTS: The proposed trademark "EFFEXOR" and designation XR are acceptable by the CDER Labeling and Nomenclature Committee. Refer to MG Chemistry review No. 4 (08-JUL-97) for other consults.

REMARKS / COMMENTS: This submission is a response to the Agency 02-MAY-97 Approvable letter and contains revised draft labeling. The sponsor does not intend to market the 100 mg strength initially and all reference to it has been deleted from the labeling. There is one change in nomenclature throughout the document. The established name was changed from "(Venlafaxine Extended Release)", which was not correct as the drug is a hydrochloride, to "(Venlafaxine Hydrochloride) Extended Release Capsules". Although the format used in the resubmission has been used in the past, the preferred format for the established name is "(Venlafaxine Hydrochloride Extended Release Capsules)", with the established name including the dosage form to distinguish it from the immediate release formulation.

CONCLUSIONS AND RECOMMENDATIONS: Recommend NDA 20-699 be approved but that sponsor be asked to revise nomenclature format. Refer question of nomenclature to PM and clinical reviewer. Nomenclature format for immediate container labels should correspond to package insert.

cc: Orig. NDA 20-699
HFD-120/Division File
HFD-120/MHeimann/07-AUG-97
HFD-120/ [redacted]
HFD-120/MGuzewska/R/D Init by: MG
HFD-810/CHOberg/JSimmons

Martha R. Heimann 8/7/97
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-699.005

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT
and
FINDING OF NO SIGNIFICANT IMPACT
for

Venlafaxine HCl
Extended Release Capsules (37.5, 75, 100, and 150 mg)

NDA 20-699

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION HFD-120
FINDING OF NO SIGNIFICANT IMPACT

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-699

Venlafaxine HCl Extended Release Capsules (37.5, 75, 100, and 150 mg)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Venlafaxine HCl Extended Release Capsules, Wyeth-Ayerst Laboratories has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31 a (a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Venlafaxine HCl is a synthetic drug indicated for the treatment of depression. Venlafaxine HCl extended-release capsules will provide a new dosage form for venlafaxine HCl which has been marketed since 1994 as Effexor® (25, 37.5, 50, 75, and 100 mg venlafaxine HCl) Tablets, as approved in NDA 20-151 (December 28, 1993). The extended-release capsule is a new dosage form for a once a day dosing regime.

The drug substance is synthesized by _____ an approved supplier of venlafaxine HCl for Effexor® Tablets. The drug product will be jointly manufactured at the Wyeth-Ayerst facility in Rouses Point, NY, and the Ayerst-Wyeth facility in Guayama, Puerto Rico.

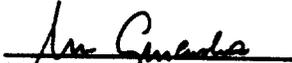
As prescribed treatment for depression, the finished drug product will be used in hospitals, clinics and the homes of patients throughout the United States. Toxicity test data indicate that no adverse environmental effects are expected at the environmental introduction concentration.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly empty used product and packaging. Information regarding disposal of production waste and returned goods is included in environmental assessment. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home-use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which includes landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

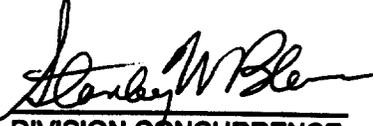
Precautions taken at the sites of manufacture of the bulk drug and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

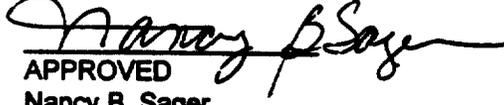
06-JUN-96
DATE


Maryla Guzewska, Ph.D.
Chemist, HFD-120

1/2/97
DATE


DIVISION CONCURRENCE
Stanley W. Blum, Ph.D.
Supervisory Chemist, HFD-120

1/17/97
DATE


APPROVED
Nancy B. Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheets (drug substance)
FOI - Releasable EA

cc: -HFD-120/Original NDA 20-699
HFD-120/Division File
HFD-120/MGuzewska
HFD-120/PDavid
HFD-120/SBlum
HFD-357/FONSI File (NDA 20-699)
HFD-357/Docket File
HFD-205/FOI Copy

ENVIRONMENTAL ASSESSMENT

NDA 20-699

Venlafaxine HCl Extended-Release Capsules (37.5, 75, 100, and 150 mg)

1. DATE:

05-JUN-96

2. NAME of APPLICANT::

Wyeth-Ayerst Laboratories

3. ADDRESS:

P.O. Box 8299, Philadelphia, PA 19101-1245

4. DESCRIPTION of PROPOSED ACTION: Approval is sought to manufacture and distribute venlafaxine HCl extended-release capsules. Four capsule strengths will be manufactured: 37.5, 75, 100 and 150 mg. Venlafaxine HCl, known as Effexor®, is currently distributed in tablets, as approved in NDA 20-151 (28-DEC-93). Venlafaxine HCl extended-release capsule is a new dosage form for the use of venlafaxine HCl in the treatment of depression.

The drug substance is synthesized by _____ an approved supplier of venlafaxine HCl for Effexor® Tablets. The drug product will be jointly manufactured at the Wyeth-Ayerst facility in Rouses Point, NY, and the Ayerst-Wyeth facility in Guayama, Puerto Rico.

As prescribed treatment for depression, the finished drug product will be used in hospitals, clinics and the homes of patients throughout the United States. The amount that is eliminated or excreted will be eliminated to municipal sewage systems. Returned, recalled, or expired goods will be disposed of in an appropriate manner according to established procedures by Wyeth-Ayerst. The goods may be collected, processed and incinerated at the following locations: Wyeth-Ayerst Laboratories, Frazer, PA (Permits No. 400516 and 15-301-071).

5. IDENTIFICATION of CHEMICAL SUBSTANCES that are the SUBJECT of the PROPOSED ACTION

Nomenclature:

Proprietary Name:

EFFEXOR®

USAN Name:

Venlafaxine HCl

Chemical Name:

(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol HCl,
or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol HCl

CAS Number:

99300-78-4 (HCl salt),

93413-69-5 (free base)

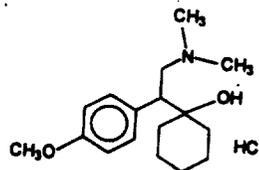
Molecular Formula:

C₁₇H₂₇NO₂ · 2 HCl

Molecular Weight:

277.41 (free base), 313.86 (HCl salt)

Structural Formula:



Physical Description:

Venlafaxine HCl is a white to off-white crystalline compound.

Excipients:

Microcrystalline cellulose, hydroxypropylmethylcellulose, ethylcellulose

Purities:

The purity of the venlafaxine HCl that will be used for preparation of the product is ≥99%. Total impurities will not be more than 0.5%.

6. INTRODUCTION of SUBSTANCES into the ENVIRONMENT: The drug substance manufacture:

The drug product will be jointly manufactured at the Wyeth-Ayerst facility in Rouses Point, NY and the Ayerst-Wyeth (AWPI) facility in Guayama, Puerto Rico.

Environmental Controls - Rouses Point, NY: All process related wash waters pass through an on-site pH neutralization system and are discharged to the Village of Rouses point Municipal Wastewater Treatment Plant (WWTP) under permit No. NY0021831. The Village Treatment Plant consists of a 1.7 MGD oxidation ditch with chlorine disinfection/oxidation which ultimately discharges to the Lake Champlain. The facility currently treats an average flow volume of approximately 800,000 gpd of which 450,000 gpd is received from the Wyeth-Ayerst manufacturing facility. The WWTP consistently achieves > 98% Biochemical Oxygen Demand (BOD) removal. Solid wastes generated during the manufacture of the drug consist of the following: product rejects, QA/QC samples and related wastes, spent HEPA filters used to purify the room air and exhaust, dust collector and vacuum system wastes. These wastes will be collected and incinerated at an EPA approved incinerator such as:

The solvents used during coating of the spheroids, methylene chloride and methanol, are recovered by condensation in a closed loop system operated at -80°C. The removal efficiency of these controls is >90% and they are operated under NYDEC permit No. 88. Recovered solvents are sent for recycle /re-use to

The coating process is the major source of air emissions requiring controls. A summary of process related air emissions, controls, permit numbers and removal efficiencies at the Rouses Point facility is presented in Table 1.

Table 1. Air Emissions at the Rouses Point Facility

EMISSION SOURCE	CONSTITUENTS	CONTROLS	EFFICIENCY	NYDEC Permit
Dust emissions (QA sample room)	Actives and Excipients	Rotoclone (wet scrubber)	99.5%	092803-0008-00030
Pharmacy (bulk dispensing)	Actives and Excipients	Fabric filter and HEPA filter	99.97%	092803-0008-00019
	Actives and Excipients	Fabric filter	99%	092803-0008-00106
		Fabric filter and HEPA filter	99.97%	092803-0008-00115
		Condenser	98% 99%	092803-0008-00080

The addition of this process is not reasonably expected to adversely impact the environment.

Environmental Controls - AWPI, Puerto Rico: All process related aqueous wastes pass through an on-site complete activated sludge plant for ozonation, treating an average daily flow of 140,000 gpd. The Waste Water Treatment Plant (WWTP) consistently achieves >98% BOD and Chemical Oxygen Demand (COD) removal. Addition of this process is not expected to cause an exceedance of the permitted average daily flow of 236,030 gpd for this discharge point. The AWPI facility discharges treated water waste to Las Mareas Bay under NPDES Permit no. PR0024724. Residual venlafaxine HCl will enter the on-site wastewater treatment system as a result of equipment wash downs. At the treatment plant, it will be subjected to biological, chemical and photochemical degradation processes before being discharged.

Dust generated during blending and packaging is removed via dust collection systems. A 99.99% removal of particulate matter is achieved prior to discharge to the atmosphere. The Environmental Quality Board in Santurce, PR has granted Air Permit #PFE-LC-30-0593-0626-I-II-0 to operate this emission source.

Solid wastes generated during the manufacture and packaging of this product consist of the following: capsule rejects and damaged product, QA/QC samples and related wastes, exhausted HEPA filters used to purify room air and exhaust. These wastes will be collected and incinerated at one of the following locations:

(Permits No. SI-93-0002, SR-0057, PFE-LC-16-0393-0305-111-0, 86-20-F-305-0994-1145-II-0, 94-46-C-163-KPU). Damaged empty bottles and packaging components will be disposed of as solid wastes at the Guayama, PR landfill.
 No solvents are used in the production of venlafaxine HCl extended release capsules at AWPI.

The Wyeth-Ayerst facility located in Rouses Point, NY and the AWPI facility located in Guayama, Puerto Rico comply with the following federal and state regulations: Clean Air Act (as amended), Federal Water Pollution Control Act of 1972, the Clean Water Act, and the Water Quality Act of 1987 (as amended), and the Resource Conservation and Recovery Act (RCRA) of 1976 (and Amendments of 1984).
 A statement of compliance with, or being on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of venlafaxine HCl extended-release capsules is provided by Wyeth.

The Material Safety Sheet for venlafaxine HCl is provided.

The Maximum Expected Emitted Concentration (MEEC) of substances released to sewage systems in the fifth year production is:

$$5.7 \times 10^{-4} \text{ ppm (0.57 ppb)}$$

The value was calculated using the following equation:

$$\text{MEEC (ppm)} = (A)(B)(C)(D)$$

where: A = 23,485 kg/yr production
 B = $1/1.115 \times 10^{11}$ liter/day entering POTWs
 C = year/365 days
 D = 10^6 mg/kg (conversion factor)

- 12. LIST of PREPARERS:** Diane L. Smith, Craig F. Seyfried, Edward Helmig, Eunice G. Kulesza (W-A), Nancy Grice McGowan (ABC Laboratories)
- 13. CERTIFICATION:** Signed on March 25, 1996 by: Craig F. Seyfried, Director, Environmental Control, Wyeth-Ayerst Laboratories
- 14. REFERENCES:** Provided
- 15. APPENDICES:** NON-CONFIDENTIAL
 A. Material Safety Data Sheet
 B. Foreign Manufacturers' Environmental Compliance Statements
 C. Rouses Point & AWPI's Environmental Compliance Statements

CONCLUSIONS and RECOMMENDATIONS: The information provided is complete and acceptable. Recommend approval of Environmental Assessment for NDA 20-699 (Venlafaxine HCl Extended Release Capsules).

MS
1/15/97

ENVIRONMENTAL ASSESSMENT INFORMATION

Venlafaxine HCl Extended-Release Capsules (37.5, 75, 100 and 150 mg)

March 25, 1996

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EXECUTIVE SUMMARY

Wyeth-Ayerst Laboratories is requesting approval for venlafaxine HCl extended-release capsules, 37.5, 75, 100 and 150 mg strengths. This Environmental Assessment, arranged as specified in the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (Nov. 1995), is part of the New Drug Application for venlafaxine HCl extended-release capsules. The immediate release form of venlafaxine HCl, Effexor[®], is a structurally novel antidepressant and is indicated for the treatment of depression. The proposed action will provide once a day dosing for this therapy choice used in the treatment of depression.

The manufacture of venlafaxine HCl extended-release capsules will not create any adverse environmental effects. The addition of this process to the Rouses Point and AWPI facilities will not cause the facilities to exceed permit limits for wastewater, air or solid wastes. No endangered or threatened species will be affected and natural resources in critically short supply will not be depleted.

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

APPEARS THIS WAY

1. DATE

March 25, 1996

2. NAME OF APPLICANT/PETITIONER

Wyeth-Ayerst Laboratories

3. ADDRESS

P.O. Box 8299
Philadelphia, PA 19101-1245

4. DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

Wyeth-Ayerst Laboratories is requesting approval of an NDA for the manufacture and marketing of venlafaxine HCl extended-release capsules. Four capsule strengths will be manufactured, 37.5, 75, 100 and 150 mg venlafaxine. Packaging of venlafaxine HCl extended-release capsules will utilize high-density polyethylene bottles and blisters. This Environmental Assessment document is part of the NDA and is arranged as specified in the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (Nov. 1995).

Effexor[®] (25, 37.5, 50, 75 and 100 mg venlafaxine HCl) Tablets have been marketed since 1994. To date, no adverse environmental impacts have been observed or reported in the field.

4.2 Need For Action

Venlafaxine HCl, a structurally novel antidepressant, is indicated for the treatment of depression. Venlafaxine extended-release capsules will provide a new dosage form for the use of venlafaxine HCl in the treatment of depression. Venlafaxine HCl, known as Effexor[®], is currently marketed. The extended-release capsule is a new dosage form for a once a day dosing regime.

4.3 Location of Production

Manufacturer of the Drug Substance
Venlafaxine HCl is synthesized by:

is an approved supplier of venlafaxine HCl for Effexor® Tablets. The bulk drug substance will be manufactured in the chemical production facility located in the industrialized area of . The population of is approximately 10,000.

Drug Product Manufacturers

for use in the 37.5 mg, 75 mg, 100 mg and 150 mg capsules occurs at:

Wyeth-Ayerst Laboratories
64 Maple Street
Rouses Point, NY 12979

The Wyeth-Ayerst facility is located in the northeast corner of New York State near the US-Canadian border and Lake Champlain. The plant is located on an 82-acre site with buildings totalling approximately 945,000 sq. ft. The main dosage form manufacturing and packaging areas are located in a contiguous portion of the facility totalling approximately 745,000 sq. ft. The facility is located in the Village of Rouses Point, New York, and the 82-acre site is bordered on the north and east by residential areas, by an elementary school on the south and railroad tracks on the west. The surrounding land has a flat topography and can be described as farmland or former farmland.

Final and packaging of the 37.5, 75, 100, and 150 mg capsules takes place at:

Ayerst-Wyeth Pharmaceuticals, Inc. (AWPI)
State Road No. 3, Km 142.1
Guayama, Puerto Rico 00784

The Ayerst-Wyeth (AWPI) plant is located in the southern region of the island of Puerto Rico, approximately 3 kilometers north of the Caribbean Sea and 2 kilometers southwest of Guayama along the north side of State Road No. 3. This region is characteristically warmer and drier than other parts of the island due to the influence of the easterly tradewinds and the proximity of the Cordillera Central to the north. According to the USDA (1977), there is no dry or wet season; however, the period between December through April is drier than the remainder of the year. Heavier rains often occur in May and October.

The area surrounding the plant is typical of a rural industrial setting consisting of

lands occupied by sugar cane fields and other manufacturing operations. The plant is bordered on the south by sugar cane fields, on the west by another pharmaceutical facility and a parking lot, on the east by an electrical substation, and on the north by Whitehall Laboratories, another pharmaceutical company owned by American Home Products. There are no private residences located near the facility. The facility is located on a 94 acre site, with one main manufacturing building occupying 700,000 square feet.

All statements made in this report regarding environmental controls, waste management, worker protection, manufacturing processes, use of resources and energy, and training emergency procedures refer to drug product manufacturing at the Wyeth-Ayerst facility in Rouses Point, NY and the Ayerst-Wyeth facility in Guayama, PR.

4.4 Locations of Drug Product Use and Disposal

As a prescribed treatment for depression, this drug will be distributed throughout the United States for oral administration. Locations of use include hospitals, clinics and the homes of patients.

The amount that is eliminated or excreted will enter the wastewater stream.

Returned, recalled, or expired goods will be disposed of in an appropriate manner according to established procedures by Wyeth-Ayerst. The goods may be collected, processed and incinerated at the following location.

Wyeth-Ayerst Laboratories
31 Morehall Road
Frazer, PA 19355

This WAL facility is located in a hilly, light industrial/commercial, suburban area with a temperate climate. The Wyeth-Ayerst facility operates under the following permits:

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
Solid Waste Incinerator Permit PADEP	400516	12/12/1984	7/4/1997
Municipal Waste Incinerator Permit PADEP	15-301-071	7/10/1991	7/30/1998

Incineration may also take place at the following location:

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
RCRA Part B Permit: Arkansas Department of Pollution Control and Ecology Hazardous Waste Management Permit.	10-H	5/26/1988	7/2/1998
Permit Modification Approval Letter	10-HR-1	2/19/1992	7/2/1998
USEPA HSWA Hazardous Waste Permit	ARD069748192	7/10/1988	7/2/1998
Arkansas Department of Pollution Control and Ecology -- Air Permit	1009-A	8/15/1990	No expiration date associated with permit
Arkansas Department of Pollution Control and Ecology -- Water Permit Renewal submitted 5/2/95 New permit pending.	NPDES AR0037800	10/28/1990	10/31/1995

Incineration may also take place at the following location:

**Delaware River
permits:**

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
RCRA Part B NJDEP Hazardous Waste Facility Permit	0809D1HP01	3/31/1989	3/31/1994
Renewal application submitted 3/1993. New permit pending.			
US EPA HSWA Permit	NJD 053 288 239	3/31/1989	3/31/1994
Renewal application submitted 3/1993. New permit pending.			

Nonhazardous waste may be incinerated at the following location.

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
NYSDEC Solid Waste Permit	1-2820-01727/ 00010-0	7/24/95	7/23/00
NYSDEC Air Permit	1-2820-01727/ 00001-0	8/7/95	8/6/96

Rejected, outdated or returned goods may also be collected and processed at:

5

for subsequent incineration at:

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
NC EMC Solid Waste Permit	01-02-I	12/31/91	Review 12/1996
Landfill Permit	13-04	8/25/95	8/25/96
NC EMC Air Quality Permit	5896R4	7/12/91	7/1/1996
NC Water Authority Waste Water Permit	0030	12/20/91	6/30/1996

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

5.a Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

Venlafaxine HCl

ii. **Brand/Proprietary Name**

Not available at this time.

iii. **Chemical Names**

(R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol
hydrochloride

or

(±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol
hydrochloride

5.b **Chemical Abstract Service (CAS) Registry Number**

99300-78-4

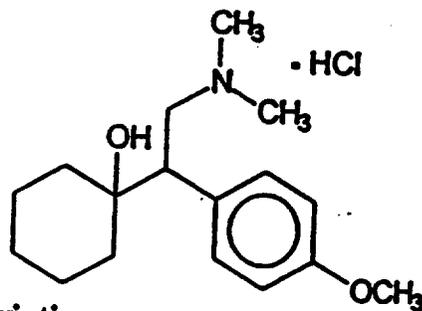
5.c **Molecular Formula**

$C_{17}H_{27}NO_2 \cdot HCl$

5.d **Molecular Weight**

313.87 g/mol

5.e **Structural Formula**



5.f **Physical Description**

Venlafaxine HCl is a white to off-white crystalline compound.

5.g **Additives**

Venlafaxine HCl contains no additives. See Appendix F for drug product

5.h Impurities

The drug substance specifications (impurities) and possible degradation products are provided in Appendix F.

5.i Material Safety Data Sheet (MSDS)

The Material Safety Data Sheet for venlafaxine HCl is provided in Appendix A.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Substances Expected To Be Emitted During Drug Substance Production and Controls Exercised

The drug substance manufacturer, identified specifically in paragraph 4.3, is located in . The synthesis of venlafaxine HCl complies with the government's environmental laws. Whenever possible, the material, byproducts and/or emissions from manufacturing are reused/regenerated/recycled back into the process. Where reuse/recycling is not feasible, the materials in question are disposed of or emitted in accordance with appropriate laws and regulations. Certifications of Environmental Compliance for the foreign manufacturer are included in Appendix B.

6.2 Substances Expected To Be Emitted During Drug Product Production and Controls Exercised

The drug product identified in Section 5 will be jointly manufactured at the Wyeth-Ayerst facility in Rouses Point, New York and the Ayerst-Wyeth (AWPI) facility in Guayama, Puerto Rico. Both facilities are identified in paragraph 4.3.

6.2.1 Environmental Control-Rouses Point, NY

The drug product manufacturing which takes place at Rouses Point, New York is a batch operation in the following sequence:

(8) transfer to the AWPI manufacturing facility. Manufacturing controls and permit information for the Rouses Point facility are described below.

Aqueous Waste

All process related wash waters pass through an on-site pH neutralization system and are discharged to the Village of Rouses Point Municipal Wastewater Treatment Plant (WWTP) under permit No. NY0021831 (expiration 5/1/98). The Village Treatment Plant consists of a 1.7 MGD oxidation ditch with chlorine disinfection/oxidation which ultimately discharges

to the Lake Champlain. The facility currently treats an average flow volume of approximately 800,000 gpd of which 450,000 gpd is received from the Wyeth-Ayerst manufacturing facility. The WWTP consistently achieves 98% and greater Biochemical Oxygen Demand (BOD) removal.

Solid Waste

Solid wastes generated during the manufacture of this product consist of the following:

- product rejects
- QA/QC samples and related wastes
- spent HEPA filters used to purify the room air and exhaust
- dust collector and vacuum system wastes

These wastes will be collected and incinerated at an EPA approved incinerator such as:

Pollution Prevention

The facility has in place a pollution prevention program. The participants are actively involved in optimizing production processes, minimizing waste generation and improving waste management practices. Solvents used in the coating process are recovered in an onsite solvent recovery system.

Solvent Waste

The solvents used during coating of the spheroids, methylene chloride and methanol, are recovered by condensation in a closed loop system operated at -80°C . The removal efficiency of these controls is $>90\%$ and they are operated under NYDEC permit #88 (expiration 10/4/97) and #104 (expiration 9/1/98).

Recovered solvents are sent for recycle/re-use to:

Recovered solvents are sent for incineration to:

Air Emission

The following is a summary of process related air emissions, controls, permit numbers and removal efficiencies at the Rouses Point facility. The coating process is the major source of emissions requiring controls.

<u>Emission Source</u>	<u>Constituents</u>	<u>Controls</u>	<u>Efficiency</u>	<u>NYDEC Permit</u>
Dust emissions QA sample room	Actives and Excipients	Rotoclone (wet scrubber)	99.5%	092803-0008- 00030 (exp 3/9/96)
Pharmacy (bulk dispensing)	Actives and Excipients	Fabric filter and HEPA filter	99.97%	092803-0008- 00019 (exp 12/1/97)
	Actives and Excipients	Fabric filter	99%	092803-008- 00106 (e x p 12/17/00)
	Actives and Excipients	Fabric filter and HEPA filter	99.97%	092803-0008- 00115 exp12/27/98)
		Condenser	98% and 99%	092803-0008 00080 (exp 8/13/00)

The addition of this process is not reasonably expected to adversely impact the environment.

6.2.2 Environmental Controls-AWPI, PR

The drug product manufacturing which takes place at the AWPI facility in Guayama, Puerto Rico, is a batch operation in the following sequence: (1) and (3) packaging. Manufacturing controls and permit information for the AWPI facility are described below.

Aqueous Waste

All process related aqueous wastes pass through an on-site complete activated sludge treatment plant with ozonation, treating an average daily flow of 140,000 gpd. The Waste Water Treatment Plant (WWTP) consistently achieves 98% and greater Biochemical Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) removal. Addition of this process is not expected to cause an exceedance of the permitted average daily flow of 236,030 gpd for this discharge point.

The AWPI facility discharges treated waste to Las Mareas Bay under NPDES Permit No. PR0024724 (expiration 11/30/95, reapplication submitted 5/27/95). The EPA inspects the AWPI WWTP annually (at a minimum). This facility is in compliance with its permit which incorporates the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439).

Residual venlafaxine HCl will enter the on-site wastewater treatment system as a result of equipment wash downs. Calculation of drug substance flow to the wastewater treatment plant and the expected removal efficiency is located in Appendix G. The venlafaxine HCl entering the treatment plant will be subjected to biological, chemical and photochemical degradation processes before being discharged.

Air Emission

Dust generated during blending and packaging is removed via dust collection systems. A 99.99% removal of particulate matter is achieved prior to discharge to the atmosphere. The Environmental Quality Board in Santurce, PR has granted Air Permit #PFE-LC-30-0593-0626-I-II-0 (expiration 2/27/2000) to operate this emission source. Periodic inspections are conducted by the local authority to ensure all control devices are operated in accordance with the permit parameters.

Solid Wastes

Solid wastes generated during the manufacture and packaging of this product consist of the following:

- capsule rejects and damaged product
- QA/QC samples and related wastes
- exhausted HEPA filters used to purify room air and exhaust

These wastes will be collected and incinerated at one of the following locations.

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
Environmental Quality Board Nonhazardous Facility Operating License			
Incineration Operating License	SI-93-0002	1/18/1993	1/19/1997
Recollection Operating License	SR-0057	1/25/95	1/19/1998
EQB PFE Air Emission Permit (new Title V Operating Permit pending)	PFE-LC-16-0393- 0305-111-0	6/25/1993	6/25/1995
ARPE Use Permit	86-20-F-305-OPC	6/1/1987	no exp. date associated with permit

<u>Permit Name</u>	<u>Permit Number</u>	<u>Issue Date</u>	<u>Expiration Date</u>
Environmental Quality Board Nonhazardous Facility Operating License Incineration Operating License	SI-93-0007	9/9/1993	9/9/1996
Transportation Operating License	SR-0028	7/22/1994	7/22/1997
EQB UIC Permit (renewal submitted 6/30/95, pending)	UIC-89-0019	8/30/1993	8/29/1995
EQB PFE Air Emission Permit	PFE-LC-13-0994- 1145-II-0	7/18/1994	3/31/1996
ARPE Use Permit	94-46-C-163-KPU	4/29/1994	no exp. date associated with permit

Damaged empty bottles and packaging components will be disposed of as solid wastes at the Guayama, Puerto Rico landfill.

Pollution Prevention

The facility has in place a pollution prevention program. The participants are actively involved in optimizing production processes, minimizing waste generation and improving waste management practices. No solvents are used in the production of venlafaxine HCl extended release capsules at AWPI.

Addition of this process is not reasonably expected to adversely impact the environment.

6.3 Citation of and Statement of Compliance with Applicable Requirements

6.3.1 Drug Substance Manufacturer

manufactures
venlafaxine HCl in accordance with all applicable environmental programs. A statement from the appropriate government authorities certifying that the facility is in full compliance with the environmental laws of the government is provided in Appendix B.

6.3.2 Drug Product Manufacturer

The pollution control devices and waste disposal methods described in paragraphs 6.2.1 and 6.2.2 serve to minimize environmental emissions from the production of venlafaxine HCl extended-release capsules.

The Wyeth-Ayerst facility located in Rouses Point, NY and the AWPI facility located in Guayama, Puerto Rico comply with the following federal and state regulations:

Clean Air Act, as Amended

The Wyeth-Ayerst facility in Rouses Point, NY operates under the air permits listed in paragraph 6.2.2. The AWPI facility operates under air Permit #PFE-LC-30-0593-0626-I-II-0 (expiration 2/27/2000). Addition of these processes are not reasonably expected to affect the compliance status of these facilities.

Federal Water Pollution Control Act of 1972, the Clean Water Act, and the Water Quality Act of 1987, as amended

The Rouses Point facility is in compliance with the Village of Rouses Point industrial wastewater permit No. NY0021831 (expiration 5/1/98) and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described in paragraph 6.2.2. This facility also operates under NYSDEC storm sewer permit No. NY0033421 (expiration 1/1/99). Addition of this process is not reasonably expected to affect the compliance status of this facility.

The AWPI facility is in compliance with NPDES permit No. PR0024724 (expiration 11/30/95, renewal submitted 5/2/95, pending) and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described in paragraph 6.2.3. Addition of this process is not reasonably expected to affect the compliance status of this facility.

The AWPI facility uses the waters generated from cooling tower blowdown and boiler blowdown to irrigate the grounds, under permit No. C-AG-84-0016 (expiration 8/31/96). The permit limit is 47,100 gallons per day with a condition of nonirrigation, when precipitation has saturated the ground, making irrigation ineffective.

Resource Conservation and Recovery Act (RCRA) of 1976 and Amendments of 1984

Solid Waste

These facilities are in compliance with all federal and state regulations governing hazardous waste generators. Any hazardous waste generated from this process will be destroyed at RCRA-permitted disposal facilities.

Nonhazardous waste generated from manufacturing and packaging this product will be disposed of at fully permitted landfills. All pharmaceutical waste and rejects are destroyed at an EPA permitted incineration facility.

Wastewater treatment sludge from the AWPI facility is subjected to aerobic digestion and dewatering (via sludge drying beds) prior to landfill disposal.

Although the EPA's "Standards for the Disposal of Sewage Sludge" (40 CFR 503) do not apply to Industrial Sludges, the AWPI facility sludge has been examined and determined to be in compliance with the "Ceiling limits" for the constituents addressed by this recently promulgated regulation.

Workplace

Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and OSHA standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure containment of chemicals and minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

Compliance Statement

Wyeth-Ayerst Laboratories states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of venlafaxine HCl extended-release capsules at its facilities in Rouses Point, NY and Guayama, PR as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of venlafaxine HCl extended-release capsules at its facilities in Rouses Point NY, and Guayama, PR.

Rouses Point and AWPI's compliance statements are found in Appendix C.

6.4 Effect of Approval on Compliance with Current Emission Requirements

The manufacture of venlafaxine HCl extended release capsules will not create any adverse environmental effects. The addition of this process the Rouses Point and AWPI facilities will not cause either facility to exceed permit limits for solid waste, wastewater or air. No endangered or threatened species will be affected and natural resources in critically short supply will not be depleted.

6.5 Concentration of Venlafaxine HCl in the Environment From Product Use and Disposal

Venlafaxine HCl extended release capsules will be distributed to locations throughout the United States for oral administration. The amount that is eliminated or excreted will enter the waste water stream. For purposes of this Environmental Assessment, the parent molecule, venlafaxine HCl, is used to evaluate environmental release mechanisms and estimated environmental concentrations.

6.5.1 Expected Introduction Concentration (EIC) From Use

The EIC for the aquatic compartment, assuming all venlafaxine HCl is used,

is evenly distributed throughout the United States per day and without metabolism or depletion mechanisms taken into account is listed below. Calculation of the EIC is found in Appendix I.

$$\text{EIC} = 5.7 \times 10^{-4} \text{ ppm}$$

The EIC for the terrestrial compartment is estimated to be zero because virtually all venlafaxine HCl remains in the aqueous compartment.

The EIC for the atmospheric compartment is estimated to be zero since venlafaxine HCl is a solid at room temperature and is expected to have a negligible vapor pressure.

6.5.2 Expected Introduction Concentration (EIC) From Disposal

The EIC from disposal is zero since all rejected product and pharmaceutical waste containing venlafaxine HCl is disposed of via incineration.

6.6 Expected Environmental Concentration (EEC)

The expected environmental concentration (EEC) of venlafaxine HCl has been calculated to be 5.7×10^{-5} mg/l. This concentration was calculated by taking the EIC (5.7×10^{-4} mg/l), a worst case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The result, 5.7×10^{-5} mg/l, is a conservative estimate of the concentration of venlafaxine HCl in the surface waters of the United States. No further depletion mechanisms have been taken into account in this calculation.

6.7 Maximum Expected Emitted Concentration (MEEC)

The maximum expected emitted concentration (MEEC) is equal to the expected environmental concentration (EEC) or the expected introduction concentration (EIC), whichever is greater. In the case of venlafaxine HCl, the MEEC is 5.7×10^{-4} mg/l.

6.8 Tier 0 Requirements

According to the CDER's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, a drug product will qualify for a Tier 0 classification if its maximum expected environmental concentration (MEEC) is less than one part per billion (1 ppb). A Tier 0 classification normally relieves the applicant from completing Environmental Assessment format items 7, 8, 9, 10, 11, and 15.

The MEEC of venlafaxine HCl, as discussed in paragraph 6.7, is 5.7×10^{-4} mg/l or 0.57 ppb, parts per billion. Thus, venlafaxine HCl qualifies as a Tier 0 drug

substance.

Although a tier 0 classification normally relieves an applicant from conducting any environmental fate and effects testing, Wyeth-Ayerst has chosen to conduct an aquatic toxicity on *Daphnia magna*. This test was conducted in order to make an environmental determination regarding the minute amount of venlafaxine HCl that may be discharged from the manufacturing facilities. The test results are reviewed in paragraph 6.9 and an environmental determination of potential toxicity is detailed in paragraph 6.10.

6.9 Aquatic Toxicity in *Daphnia magna*

The acute toxicity (EC50) and No-Observed-Effect Concentration (NOEC) of venlafaxine HCl to daphnids (*Daphnia magna*) were estimated using static acute renewal test conditions and a 48-hour exposure period. The test was conducted following FDA TAD §4.08.² The EC50 is defined as the concentration of the test article in dilution water which causes immobilization of 50% of the exposed test population after a fixed period of time. The NOEC is defined as the highest concentration tested at and below which there were no toxicant-related immobilization or physical and behavioral abnormalities (e.g. lethargy), when compared to control organisms. This information is often used as a relative indicator of potential acute hazards resulting from release of the test article into aquatic environments.

Four replicate 1000 mL test vessels were used for each treatment level and the controls. Daphnids, < 24 hours old, were impartially distributed one at a time to each vessel of each concentration and the controls (five daphnids per replicate). At 24 hours of exposure, all mobile daphnids in each aged exposure solution were carefully transferred to an appropriately labeled beaker containing freshly prepared exposure solution using a wide bore pipet. The number of immobilized daphnids in each replicate test vessel was recorded at 24 and 48 hours of exposure.

The mean measured concentrations tested (0-, 24- and 48-hour analyses) and the corresponding immobilization data were used to estimate the 24- and 48-hour median effect concentrations (EC50) and 95% confidence intervals. These results indicate that venlafaxine HCl has a 48-hour EC50 value of 38 mg/l and a No-Observed-Effect Concentration through 48-hours is 4.8 mg/l.

The mean measured concentration of venlafaxine HCl tested, the corresponding cumulative percent and number of immobilized daphnids and the observations made during the definitive test are summarized in the following table.

Mean Measured Concentration (mg/L)	Cumulative Percent of Immobilized Organisms ^a									
	24-Hour					48-Hour				
	A	B	C	D	Mean	A	B	C	D	Mean
Control	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)	0
0.56	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)	0
1.1	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)	0
2.3	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)	0
4.8	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)	0
9.9	0 (0)	0 (0)	0 (0)	0 (0)	0	20 (1)	0 (0)	0 (0)	0 (0)	5 ^b
17	0 (0)	20 (1)	0 (0)	20 (1)	10 ^b	0 (0)	20 (1)	0 (0)	60 (3)	20 ^b
38	20 (1)	0 (0)	20 (1)	40 (2)	20 ^c	40 (2)	40 (2)	20 (1)	40 (2)	35 ^c
78	20 (1)	40 (2)	20 (1)	0 (0)	20 ^c	80 (4)	80 (4)	100 (5)	100 (5)	90 ^c

^a The actual number of immobilized daphnids is presented in parentheses.

^b Several of the surviving daphnids were observed to exhibit lethargic swimming behavior.

^c All of the mobile daphnids were observed to be lethargic.

The established EC50 values and the No-Observed-Effect Concentrations (NOEC) are listed in the following table.

	EC50 ^a (mg/L)	95% Confidence Interval	
		Lower ^a (mg/L)	Upper ^a (mg/L)
AS SALT			
24-Hour ^a	> 78	---	---
48-Hour ^b	38	30	51
NOEC Through 48 Hours ^a = 4.8 mg/L			
AS FREE BASE			
24-Hour ^a	> 69	---	---
48-Hour ^b	34	26	46
NOEC Through 48 Hours ^a = 4.2 mg/L			

^a EC50 value was empirically estimated to be greater than the highest mean measured concentration tested, therefore, the corresponding 95% confidence interval could not be calculated.

^b EC50 value (corresponding 95% confidence interval) was calculated by probit analysis.

A report of this study is included in Appendix D.

6.10 Potential Toxicity Effects

As defined in 21 CFR 25.15(b)(6), a substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment, i.e., either at any point of entry or any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes, exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level-MEL) or exceeds 1/100 of the concentration that causes 50% mortality in a test organism species (LD₅₀ or LC₅₀), whichever concentration is less. This concentration is defined as the "Criterion Concentration" (CC).

The Criterion Concentration for venlafaxine HCl is 0.38 mg/L. Review of the following toxicological data was used to determine the Criterion Concentration. Aquatic toxicity testing of *Daphnia magna* has resulted in a No-Observed-Effect Concentration (NOEC) or minimum effect level (MEL) of 4.8 mg/L of venlafaxine HCl. The same test resulted in a 48-hour median effect concentration (EC50) of 38

mg/L. Taking into consideration the conditions of the definition of the Criterion Concentration, 1/100 of the LD50, in this case the EC50 of *Daphnia magna*, is 0.38 mg/L. The Criterion Concentration was determined to be 0.38 mg/L by choosing the most conservative of these toxicological values.

6.10.1 Rouses Point, NY

The concentration of venlafaxine HCl in Rouse Point's local surface water, the Lake Champlain, is calculated to be 0.036 mg/l. See Appendix G for calculations. This discharge is due to the possibility of minute amounts of venlafaxine HCl being discharged to the wastewater treatment plant during manufacture of the drug product. The Criterion Concentration in this case is 0.38 mg/l. Therefore, the discharge due to possible manufacturing loss is less than the Criterion Concentration and is considered non-toxic by definition.

6.10.2 AWPI, PR

The concentration of venlafaxine HCl in AWPI's local surface water, Las Mareas Bay, is calculated to be 0.061 mg/l. See Appendix G for calculations. This discharge is due to the possibility of minute amounts of venlafaxine HCl being discharged to the wastewater treatment plant during manufacture of the drug product. The Criterion Concentration in this case is 0.38 mg/l. Therefore, the discharge due to possible manufacturing loss is less than the Criterion Concentration and is considered non-toxic by definition.

12. LIST OF PREPARERS

Diane L. Smith, Ph.D.
Wyeth-Ayerst Laboratories

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ABC Laboratories, Inc

Craig F. Seyfried
Wyeth-Ayerst Laboratories

Edward Helmig
Wyeth-Ayerst Laboratories

Eunice G. Kulesza
Wyeth-Ayerst Laboratories

The preparers' resumes are provided in Appendix E.

13. CERTIFICATION

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of Wyeth-Ayerst Laboratories.

Date March 25, 1996

Signature Craig F. Seyfried

Craig F. Seyfried
Director, Environmental Control
Wyeth-Ayerst Laboratories

14. REFERENCES

1. Pharmaceutical Manufacturers Association, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA*. July 1991.
2. U.S. Food and Drug Administration, *Environmental Technical Assistance Handbook*, PB87-175345, U.S. Department of Commerce National Technical Information Service, Springfield, VA, 1987.
3. U.S. Environmental Protection Agency (Toxic Substances Control Act Test Guidelines, Chemical Fate Testing Guidelines, 40 CFR 796.3140, "Anaerobic biodegradability of Organic Chemicals").
4. Center for Drug Evaluation and Research, *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, Nov. 1995.

15. APPENDICES

NON-CONFIDENTIAL

- | | |
|------------|---|
| Appendix A | Material Safety Data Sheet |
| Appendix B | Foreign Manufacturers' Environmental Compliance Statements |
| Appendix C | Rouses Point & AWPI's Environmental Compliance Statements |
| Appendix D | Venlafaxine HCl-Acute Toxicity To Daphnids (<i>Daphnia magna</i>) Under Static Conditions |
| Appendix E | Preparers' Resumes |

CONFIDENTIAL

Appendix F	Drug Product Information
Appendix G	Calculation of Wastewater Treatment Plant Loading and Removal
Appendix H	Five Year Market Estimates
Appendix I	Expected Introduction Concentration (EIC) Calculation
Appendix J	Wyeth-Ayerst General Technical Report 13517, <i>Stability of WY-45030 HCl Drug Substance Under Stress Storage Conditions.</i>
Appendix K	Wyeth-Ayerst General Technical Report 18748, <i>Preformulation Report of Venlafaxine Hydrochloride, Part I: Physicochemical Characteristics.</i>
Appendix L	Wyeth-Ayerst General Technical Report 19169, <i>Preformulation Report of Venlafaxine HCl, Part II: Chemical Degradation Studies.</i>

APPENDIX A

Material Safety Data Sheet

OCCUPATIONAL HEALTH SERVICES, INC.
11 WEST 42ND STREET, 12TH FLOOR
NEW YORK, NEW YORK 10036
1-800-445-MSDS (1-800-445-6737) OR
1-212-789-3535

FOR EMERGENCY SOURCE INFORMATION
CONTACT: 1-615-366-2000 USA

SUBSTANCE IDENTIFICATION

SUBSTANCE: VENLAFAXINE HYDROCHLORIDE

CAS NUMBER: 99300-78-4

TRADE NAMES/SYNONYMS:

CYCLOHEXANOL, 1-(2-(DIMETHYLAMINO)-1-(4-METHOXYPHENYL)ETHYL)-,
HYDROCHLORIDE;
1-(2-(DIMETHYLAMINO)-1-(4-METHOXYPHENYL)ETHYL)CYCLOHEXANOL,
HYDROCHLORIDE;
WY 45030; C17H28ClNO2; OHS33482

CHEMICAL FAMILY:

Halogen compound, alicyclic

MOLECULAR FORMULA: C17-H27-N-O2.H-CL

MOLECULAR WEIGHT: 313.87

CERCLA RATINGS (SCALE 0-3): HEALTH=U FIRE=1 REACTIVITY=0 PERSISTENCE=1
NFPA RATINGS (SCALE 0-4): HEALTH=U FIRE=1 REACTIVITY=0

COMPONENTS AND CONTAMINANTS

COMPONENT: VENLAFAXINE HYDROCHLORIDE
CAS# 99300-78-4

PERCENT: 100.0

OTHER CONTAMINANTS: None.

EXPOSURE LIMITS:

No occupational exposure limits established by OSHA, ACGIH, or NIOSH.

PHYSICAL DATA

DESCRIPTION: White, crystalline powder. MELTING POINT: not available

SPECIFIC GRAVITY: not available SOLUBILITY IN WATER: not available

FIRE AND EXPLOSION DATA

FIRE AND EXPLOSION HAZARD:

Slight fire hazard when exposed to heat or flame.

Dust-air mixtures may ignite or explode.

FIREFIGHTING MEDIA:

Dry chemical, carbon dioxide, water spray or regular foam (1993 Emergency Response Guidebook, RSPA P 5800.6).

For larger fires, use water spray, fog or regular foam (1993 Emergency Response Guidebook, RSPA P 5800.6).

FIREFIGHTING:

Move container from fire area if you can do it without risk. Do not scatter spilled material with high-pressure water streams. Dike fire-control water for later disposal (1993 Emergency Response Guidebook, RSPA P 5800.6, Guide Page 31).

Use agents suitable for type of surrounding fire. Avoid breathing hazardous vapors, keep upwind.

TOXICITY

VENLAFAXINE HYDROCHLORIDE:

CARCINOGEN STATUS: None.

ACUTE TOXICITY LEVEL: No data available.

TARGET EFFECTS: No data available.

AT INCREASED RISK FROM EXPOSURE: Persons with pre-existing respiratory, skin and eye disorders.

ADDITIONAL DATA: Venlafaxine hydrochloride is an antidepressant and a physiologically active drug substance.

HEALTH EFFECTS AND FIRST AID

INHALATION:**VENLAFAXINE HYDROCHLORIDE:**

ACUTE EXPOSURE- No data available.

CHRONIC EXPOSURE- No data available.

FIRST AID- Remove from exposure area to fresh air immediately. Perform artificial respiration if necessary. Keep person warm and at rest. Treat symptomatically and supportively. Get medical attention immediately.

SKIN CONTACT:**VENLAFAXINE HYDROCHLORIDE:**

ACUTE EXPOSURE- No data available.

CHRONIC EXPOSURE- No data available.

FIRST AID- Remove contaminated clothing and shoes immediately. Wash with soap or mild detergent and large amounts of water until no evidence of chemical remains (at least 15-20 minutes). Get medical attention immediately.

EYE CONTACT:**VENLAFAXINE HYDROCHLORIDE:**

ACUTE EXPOSURE- No data available.

CHRONIC EXPOSURE- No data available.

FIRST AID- Wash eyes immediately with large amounts of water or normal saline, occasionally lifting upper and lower lids, until no evidence of chemical remains (at least 15-20 minutes). Get medical attention immediately.

INGESTION:
VENLAFAXINE HYDROCHLORIDE:
ACUTE EXPOSURE- No data available.
CHRONIC EXPOSURE- No data available.

FIRST AID- If conscious, immediately induce vomiting by giving 2-4 glasses of water and touching finger to back of throat. Repeat until vomited fluid is clear. Syrup of ipecac may be used, followed by activated charcoal. Get medical attention immediately.

ANTIDOTE:
No specific antidote. Treat symptomatically and supportively.

REACTIVITY

REACTIVITY:
Stable under normal temperatures and pressures.

INCOMPATIBILITIES:
VENLAFAXINE HYDROCHLORIDE:
OXIDIZERS (STRONG): Fire and explosion hazard.

DECOMPOSITION:
Thermal decomposition products may include toxic and corrosive fumes of hydrogen chloride and oxides of carbon and nitrogen.

POLYMERIZATION:
Hazardous polymerization has not been reported to occur under normal temperatures and pressures.

STORAGE AND DISPOSAL

Observe all federal, state and local regulations when storing or disposing of this substance.

****Storage****

Store away from incompatible substances.

CONDITIONS TO AVOID

May burn but does not ignite readily. Avoid contact with strong oxidizers, excessive heat, sparks, or open flame.

SPILL AND LEAK PROCEDURES

OCCUPATIONAL SPILL:
Sweep up and place in suitable clean, dry containers for reclamation or later disposal. Do not flush spilled material into sewer. Keep unnecessary people away.

PROTECTIVE EQUIPMENT

VENTILATION:

Provide local exhaust ventilation. Ventilation equipment should be explosion-proof if explosive concentrations of dust, vapor or fume are present.

RESPIRATOR:

The following respirators are recommended based on information found in the physical data, toxicity and health effects sections. They are ranked in order from minimum to maximum respiratory protection. The specific respirator selected must be based on contamination levels found in the work place, must be based on the specific operation, must not exceed the working limits of the respirator and must be jointly approved by the National Institute for Occupational Safety and Health and the Mine Safety and Health Administration (NIOSH-MSHA).

Any dust and mist respirator.

Any air-purifying respirator with a high-efficiency particulate filter.

Any powered air-purifying respirator with a dust and mist filter.

Any powered air-purifying respirator with a high-efficiency particulate filter.

Any type 'C' supplied-air respirator operated in the pressure-demand or other positive pressure or continuous-flow mode.

Any self-contained breathing apparatus.

FOR FIREFIGHTING AND OTHER IMMEDIATELY DANGEROUS TO LIFE OR HEALTH CONDITIONS:

Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode.

Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode.

CLOTHING:

Employee must wear appropriate protective (impervious) clothing and equipment to prevent repeated or prolonged skin contact with this substance.

GLOVES:

Employee must wear appropriate protective gloves to prevent contact with this substance.

EYE PROTECTION:

Employee must wear splash-proof or dust-resistant safety goggles to prevent eye contact with this substance.

Emergency eye wash: Where there is any possibility that an employee's eyes may be exposed to this substance, the employer should provide an eye wash fountain within the immediate work area for emergency use.

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CREATION DATE: 05/09/94 REVISION DATE: 06/30/94

APPENDIX B

Foreign Manufacturer's Compliance Statements

Citations

Siegfried Chemie AG, Zofingen, Canton of Aargau, Switzerland.

All the Siegfried Chemie facilities in Switzerland must be in compliance with the restriction on the release of industrial wastes into the local sewer system and on the release of volatile organic substances into the atmosphere as set forth in the regulations of the Swiss Authorities:

Air Citations - Federal Air Pollution Control Regulation = „Luftreinhalteverordnung“ (LRV) 814.318.142.1 (16th Dezember, 1985; latest edition 1st July, 1993).

Water Citations - Federal Regulation to Introduce Waste Water into the Local Sewer System = „Verordnung über Abwassereinleitungen“ 814.225.21 (8th Dezember, 1975; latest edition 1st January, 1993).

Solids Citations - Federal Regulation for the Transport and Disposal of Special Waste = „Verordnung über den Verkehr mit Sonderabfällen“ (VVS) 814.014 (12th November, 1986; latest edition 1st January, 1993).

Attestation

We attest herewith the correctness of the preceding citations.

Zofingen, July 29th 1994



The municipal Council of Zofingen

The President:

Urs Locher

The Secretary:

Arthur Senn

APPENDIX C

Rouses Point & AWPI's Environmental Compliance Statements

GENERAL COMPLIANCE STATEMENT

Ayerst Laboratories, Inc. (A.K.A. Wyeth Ayerst Laboratories) states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Venlafaxine HCl extended release capsules at its facilities in Rouses Point, NY as well as emission requirements set forth in applicable, federal, state, and local statutes and regulations applicable to the production of Venlafaxine HCl extended release capsules at its facilities in Rouses Point, NY.

 10/19/95

William E. Brooks
Managing Director

GENERAL COMPLIANCE STATEMENT

Ayerst-Wyeth Pharmaceuticals, Inc., states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of **Venlafaxine HCl Extended Release Capsules** at its facilities in Guayama, Puerto Rico, as well as emission requirements set forth in applicable, federal, state, and local statutes and regulations applicable to the production of **Venlafaxine HCl Extended Release Capsules** at its facilities in Guayama, Puerto Rico.



Mariano Martinez-Mora
Vice President and General Manager
Ayerst-Wyeth Pharmaceuticals, Inc.
Guayama, P.R. Facility

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

PHARMACOLOGY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Original Summary

NDA No.: 20699

Submission Date: 5/24/96

Review Date: 2/5/97

Drug: Venlafaxine ER

Sponsor: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Reviewer: T.D. Steele

Indication: Depression

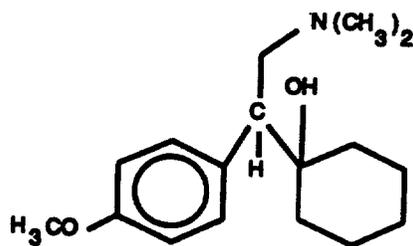
Chemical Information:

Name(s): 1-[2-dimethylamino-1(4-methoxyphenyl)ethyl] cyclohexanol

Empirical Formula: C₁₇H₂₇NO₂ HCl

Molecular Weight: 313.87

Structure:



venlafaxine HCl

Previous INDs/NDAs:

Preclinical Pharmacology/Toxicology Studies Reviewed:

Per an agreement between the sponsor and FDA, reference is made to NDA 20,151 for supportive nonclinical studies of the drug substance (Effexor, venlafaxine HCl). No additional nonclinical studies were required to support this NDA because the excipients in the ER preparation are GRAS, and the new formulation is bioequivalent to the approved formulation (per Dr. Ibrahim of HFD-860).

Labeling:

The labeling has been reviewed. The labeling that refers to nonclinical pharmacology and toxicology studies is essentially identical to the labeling for the approved formulation with one exception (as identified by the Medical Officer, Dr. Dubitsky). The original review of the mutagenicity findings in question (i.e., clastogenic response to the metabolite O-desmethylvenlafaxine in the *in vivo* rat bone marrow chromosomal aberration assay) indicates that the response was weak, but warranted inclusion in the labeling. Unless the sponsor has conducted and submitted studies that support their proposed revision, the following change should be made:

Mutagenicity section. Line 7:

clastogenic response in the *in vivo* chromosomal..."

"There was a..."

[It is also noted that a weak positive transformation response to ODV in the absence of metabolic activation in the *in vitro* BALB/c-3T3 assay was recommended (by the pharmacologist), but not included, in Effexor labeling.]

Mutagenicity section. Line 3:

"Venlafaxine was also not..."

Recommendation:

1. The NDA is approvable.
2. The Mutagenicity section of Labeling requires modification.

*T.L. Comment:
Change line 7 of the
mutagenicity section
to read: "ODV
elicited a clastogenic
change line 3 as
noted above
GGJ 2/7/97*


Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20-699 ²

c.c: /Division File, HFD-120

/G. Fitzgerald, Ph.D.

/G. Dubitsky, M.D.

/T. Laughren, M.D.

/P.David, R.Ph.

/T.D. Steele, Ph.D.

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