CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #20,699

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor XR (venlafaxine HCl) Extended Release Capsules
Indication:	Depression
Material Reviewed:	Response to 5/2/97 Approvable Letter
Date Submitted:	May 15, 1997
Date Received:	May 16, 1997

I. Background

NDA 20,699, for Effexor XR (venlafaxine hydrochloride) Extended Release Capsules in the treatment of depression, was submitted on May 16, 1996. An approvable letter was issued on May 2, 1997, and identified the following clinical issues to be addressed before final approval:

1) creation of mutually acceptable product labeling.
2) safety update.
3) foreign regulatory status update.
4) world literature update.
5) status update on a Phase 4 commitment to conduct a

This submission contains the safety, foreign regulatory, and world literature updates (Tabs 1, 2, and 3, respectively) as well as confirmation that a using Effexor XR, is underway, with the final study report expected to be available in early 1999. A response to the Agency's proposed labeling will be submitted separately.

II. Safety Update

A. Description of Database

As of 12/31/95, which was the latest cutoff date for safety data in the original NDA submission, the sponsor's development program for Effexor XR consisted of a total of 17 studies either completed or in progress. Eleven of these 17 were

completed and all safety data from these studies was included in the original NDA submission.[1]

The remaining 6 studies were ongoing as of 12/31/95. Four of these studies (101, 210, 211, and 360) were still blinded and only serious adverse events up to this cutoff were reported. The remaining 2 trials were open label Phase 3 extension studies (365 and 369). All safety data from these latter two studies was included in the original submission up to 8/31/95 (365) and 9/30/95 (369); additionally, all serious adverse events up to 12/31/95 were reported.

Since the 12/31/95 cutoff date for the original NDA submission and as of the 9/30/96 cutoff for this safety update, studies 365 and 369 have been completed; studies 101, 210, 211, and 360 are still in progress and remain blinded; and 10 new studies have been initiated and are still blinded and ongoing. All 16 studies contributing data to this update are tabulated in Appendix 1.

Thus, this update encompasses information up to 9/30/96 on deaths, other serious adverse events,[2] and discontinuations due to adverse events from studies 365 and 369 which were not reported in the original NDA submission. For the fourteen ongoing, blinded studies, information from only 3- and 10-day IND safety reports to 9/30/96 are included in this update.

B. Deaths

There was one death during the update interval: patient 37817-009 was an 89 year old female who began blinded treatment in the European Phase III study 378. On the second day of treatment, she experienced the sudden onset of palpitations and chest pain, resulting in hospitalization. The study drug was discontinued the next day. A myocardial infarction was ruled out and she was discharged with a diagnostic impression of cardiac arrhythmia. She subsequently died of bronchopneumonia, about 2 months after study drug discontinuation. Her medical history was remarkable for untreated mild hypertension and atrial fibrillation, treated with digoxin. The palpitations and chest were possibly related to study drug; however, the cause of death, bronchopneumonia, is felt to be unlikely related to drug.

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[1]The 11 completed studies were: 127, 134, 136, 138, 139, 143, 144, and 145 (Phase 1) as well as 208, 209, and 367 (Phase 3).

[2]The sponsor applied the same criteria for "serious" as in the original submission.

C. Other Serious Adverse Events

A total of 26 patients experienced other serious adverse events in the update interval. Narrative summaries for these patients were reviewed and information is summarized by patient in Appendix 2. Eight of these serious events were not reported in the original Effexor XR safety database and, thus, might be considered unexpected; these events are discussed below in more detail.

Three patients experienced benign tumors:

Patient 36528-002 was a 41 year old male who complained of new onset left thigh pain on the first day of treatment with venlafaxine ER 75 mg/day. Tomography was done about 3½ months later, revealing a cystic structure in the proximal diaphysis of the left femur. No biopsy was performed and a **benign bone tumor** was diagnosed; no intervention was undertaken and the patient continued in the study for another 4 months.

Patient 36530-004 was a 49 year old female was treated with venlafaxine ER 75 mg/day for about 11 months when a biopsy of a right breast mass revealed an **adenofibroma**. The patient went on to complete the study and the tumor was surgically removed post-study.

Patient 36906-005 was a 42 year old woman with a history of fibrocystic breast disease who reported a left **breast mass** after 369 days of treatment with venlafaxine ER 75 mg/day. She completed the study the next day and a subsequent biopsy revealed no malignant cells. No further data was provided.

Patient 36532-009 was a 52 year old woman who was treated with venlafaxine ER 150 mg/day for about 8 months when an ophthalmologist detected bilateral **closed angle glaucoma**, which was not present pre-study. This was treated with timolol eye drops and study drug was continued for another 2 weeks before premature discontinuation related to this finding.

Patient 36533-008 was a 49 year old male with a history of appendectomy, non-insulin dependent diabetes mellitus, alcohol abuse, and hemorrhoids. After approximately 5 months of treatment with venlafaxine ER 75 mg/day, he was hospitalized for abdominal pain and was diagnosed with **diverticulitis**. This was treated medically and venlafaxine ER was temporarily discontinued; he subsequently completed the study about 6 months later.

Patient 36537-003 was a 74 year old female with a history of hypertension, hyperlipidemia, and coronary insufficiency who received multiple concomitant medications. After about one

year of treatment with venlafaxine ER, atrial flutter was diagnosed and, subsequently, **atrial fibrillation.** She was hospitalized for electroshock conversion, which was successful in reestablishing a sinus rhythm. Atrial fibrillation reappeared after study completion.

Patient 36903-018 was a 29 year old obese female, with a family history of glucose intolerance, who was discovered to have an **elevated glucose level** at her post-study visit (224 mg/dl, baseline=134 mg/dl). She withdrew from the study due to inability to keep appointments and no follow-up information was available.

Patient 36904-006 was a 41 year old man who abruptly discontinued venlafaxine ER due to sexual dysfunction after 5 months of treatment. He reported hearing **auditory hallucinations** beginning 3 days after drug discontinuation. He was started on Prozac and the hallucinations resolved a day later.

From data such as that submitted in this update, it is virtually impossible, except for rare adverse events occurring in well documented cases, to draw any solid inference regarding causality. Nonetheless, some of these events appear unlikely to be causally related to venlafaxine ER, specifically the bone tumor (symptoms present on day 1 of treatment), diverticulitis (negative rechallenge), atrial fibrillation (reemergence after drug stopped), and auditory hallucinations (began after drug stopped).

While causality in the remaining 4 cases cannot be as easily minimized, most of these events cannot be easily ascribed to drug either. The encapsulated adenoma reported in patient 36530-004 is the most common benign tumor of the female breast and its occurrence in this database cannot be considered highly unusual. The breast mass in patient 36906-005 may be more likely secondary to fibrocystic breast changes than drug. The hyperglycemia noted in patient 36903-018 is confounded by obesity, a family history of glucose intolerance, and the possible ingestion of carbohydrates prior to blood collection. The closed angle glaucoma detected in patient 36532-009 may be related to venlafaxine ER-associated mydriasis[3] in a patient with a shallow anterior chamber; glaucoma will be listed in the "Other Events" table of Effexor XR labeling by virtue of its occurrence in the Effexor premarketing clincial trials database.

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[3]There was some degree of association between venlafaxine ER and mydriasis in the short-term, placebo-controlled studies (3% of drug and 0% of placebo patients reported mydriasis).

D. Dropouts due to Adverse Events

Listings of adverse events that led to dropout in patients from studies 365 and 369 during the update interval were reviewed (i.e., Tables 1 and 2, respectively, under Tab 1 of this submission). Only one event, which had not been previously reported with venlafaxine ER, led to dropout:

Patient 36909-004 was a 55 year old female who was treated with venlafaxine ER 375 mg/day when, after 276 days of treatment, she dropped out due to an **elevated TSH level**. The reason for checking a TSH level is unclear from the limited data provided.

The clinical significance of this finding is unknown: neither abnormalities in T3 or T4 levels nor clinical symptoms of hypothyroidism are mentioned. Thyroid functioning was not routinely monitored in the Effexor XR development program and a drug relationship cannot be entirely excluded, particularly in view of: 1) the small number of patients likely to have received a relatively high dose, such as this patient; 2) limited long-term clinical trials data; and 3) the possibility of subtle, undetected effects without frank symptoms of thyroid dysfunction in a larger number of patients. In any event, this isolated finding cannot provide compelling evidence that venlafaxine ER adversely affects thyroid status.

E. Safety Update Conclusions

No new hazard, which is judged to be reasonably attributable to venlafaxine ER, has been identified in this update.

III. Foreign Regulatory Status Update

Marketing applications for Effexor XR capsules have been submitted in 19 foreign countries (see Appendix 3). Final approval has not been granted in any market and, thus, no foreign labeling is submitted for review. No deficiency letters have been issued by any regulatory agency.

IV. World Literature Update

No literature articles had been published at the time of the original NDA submission. A subsequent literature search was conducted by Ruthanne T. Henner, Principal Information Scientist, Information Services Section, Wyeth-Ayerst Research, to identify published papers relevant to Effexor XR as of 3/17/97. This process used the OVID System to search the following databases:

- MEDLINE.
- BIOSIS.
- EMBASE.
- DERWENT.

Four publications were identified and are provided under Tab 3 of the submission. Loren Aguiar, M.D., the Effexor XR Medical Monitor, has signed a warrant that these articles were thoroughly reviewed and that there are no findings that would adversely affect conclusions about the safety of Effexor XR.

V. Conclusions

The safety, foreign regulatory, and world literature updates contained in this submission support the previous conclusion that Effexor XR is reasonably safe under the conditions of use stated in our proposed labeling.

Approval of this NDA must await submission of and agreement with final product labeling.

Gregory M. Dubitsky, M.D.
May 28, 1997

cc: NDA #20,699
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

9-12-97
I agree that this NDA can now be approved.
See 9-12-97 memo to file for more detailed response
Laughren MD
TL, PSP

APPENDIX 1: Studies Included in the Safety Update

Study	Phase	Indication
Completed Studies		
365	III	Depression
369	III	Depression
Ongoing Studies		
153*	I	Clin Pharmacology
156**	I	Clin Pharmacology
210	II	GAD
211	II	Depression
214	II	GAD
215	II	Pain
216	II	Pain
217	II	Depression
218	II	GAD
360	III	Depression
370	III	Depression
377	III	GAD
378	III	GAD
670	III	Depression

* Formerly 101.
** Formerly 102.

APPENDIX 2: Other Serious Adverse Events

Patient #	Age	Sex	Dose (mg/d)	Onset (days)	Event
36501-006	36	F	150	114	Head injury
36505-302	49	F	75	272	Neck injury
36519-002	26	F	75	325	Suicide attempt
36524-002	30	F	150	256	Pregnancy (normal infant)
36526-003	52	F	150	150	Social hospitalization
36528-002	41	M	75	1	Benign bone tumor
36528-004	44	M	75	371	↑ liver enzymes
36529-001	82	F	150	149	Head trauma
36529-005	36	M	150	227	Accidental CO poisoning
36530-004	49	M	75	326	Benign breast tumor
36532-001	27	F	150	244	Suicide attempt
36532-009	52	F	150	250	Closed angle glaucoma
36533-008	49	M	75	155	Diverticulitis
36534-002	54	M	75	215	Hosp. for arthroscopy
36537-003	74	F	150	347	Atrial fibrillation
36537-006	25	F	75	386	Hosp. for violent headache
36537-007	23	F	150	100	Foot trauma
36901-015	70	M	300	352	Struck by vehicle
36903-016	28	F	0	+8	Syncope post-study
36903-018	29	F	?	247	↑ blood glucose
36904-006	41	M	0	+3	Hallucinations post-study
36906-005	42	F	75	369	Benign breast mass
36906-010	44	M	375	215	Accidental injury
36907-013	22	F	375	296	Hosp. for suicidal ideation
36909-013	37	F	150	206	Memory impairment
36024-009	64	M	75	4	Palpitations, syncope

+ indicates number of days post-study.

APPENDIX 3: Foreign Marketing Applications

Austria	France	Spain
Australia	Germany	Sweden
Belgium	Greece	Switzerland
Brazil	Italy	Turkey
Canada	Mexico	United Kingdom
Denmark	Netherlands	
Finland	New Zealand	

Review and Evaluation of Clinical Data
NDA #20,699

Sponsor:	Wyeth-Ayerst Research
Drug:	Effexor XR (Venlafaxine HCl Extended Release Capsules)
Indication:	Depression
Material Reviewed:	Response to Approvable Letter: Revised Draft Labeling
Date Submitted:	June 12, 1997
Date Received:	June 13, 1997

I. Background

NDA 20,699 for Effexor XR (Venlafaxine HCl Extended Release Capsules) was submitted on May 16, 1996. An approvable action letter was issued on May 2, 1997, and included draft labeling that was acceptable to the Agency. The following clinical areas were to be addressed by the sponsor prior to final approval:

1) final product labeling.
2) safety update.
3) foreign regulatory status update.
4) world literature update.
5) status update on a Phase 4 commitment to

Items 2-5 were adequately addressed in a subsequent submission dated May 15, 1997, which was reviewed by the undersigned on May 28, 1997. The current submission contains the sponsor's revision of the Agency's proposed labeling. Proposed changes to the clinical sections of the Agency's draft product labeling are summarized and discussed below.

II. Labeling Revision

A. GENERAL

Throughout labeling, the sponsor had modified the phrase "Effexor XR (venlafaxine extended release)" to "Effexor XR (venlafaxine hydrochloride) extended release capsules." According to the chemistry reviewer, the preferred format is "Effexor XR (Venlafaxine Hydrochloride Extended Release Capsules)," with the

dosage form enclosed within the parentheses to more clearly distinguish it from the immediate release formulation. I concur and recommend that the latter format be used.

Also, the sponsor changed the term "venlafaxine ER" to "Effexor XR" for consistency with the rest of labeling. This is acceptable.

B. CLINICAL PHARMACOLOGY

Clinical Trials

The effects of Effexor XR on certain HAM-D factors were added by the sponsor: the anxiety factor, cognitive disturbance factor (items 2, 3, 9, 19, 20, and 21), and retardation factor (items 1, 7, 8, and 14). Also, the CGI-improvement score results were included. It was clarified in a 7/16/97 telephone with Ken Bonk of W-A Regulatory Affairs that the term "anxiety factor" is intended to refer to both the anxiety/somatization factor (items 10, 11, 12, 13, 15, and 17) and the psychic anxiety score (item 10) of the 21-item HAM-D. Pertinent data are summarized in Appendix 1 of this review and do support these statements. Thus, their proposal is acceptable with one exception: it is recommended that the term "anxiety factor" be replaced with "anxiety/somatization factor" and that the term "psychic anxiety score" be added to more accurately reflect the actual factors analyzed.

Also, a description of the results of the clinical trial of Effexor in inpatients with major depression and melancholia has been added to correspond to the insertion of those study results in the **DOSAGE and ADMINISTRATION** section. This is acceptable.

C. INDICATIONS AND USAGE

The wording that references earlier descriptions of clinical trials has been changed from "under **CLINICAL PHARMACOLOGY**" to "see **Clinical Trials.**" This is acceptable.

Further, the paragraph indicating the lack of efficacy data in hospitalized depressed patients has been replaced by a statement that the efficacy of the IR formulation was established in depressed inpatients. This is acceptable.

D. WARNINGS

Sustained Blood Pressure

The sponsor has reworded the introductory sentence to indicate that venlafaxine is associated with sustained increases in blood pressure in some patients, replacing our proposed statement that venlafaxine can cause sustained increases in blood pressure. This is acceptable.

E. PRECAUTIONS

General

Insomnia and Nervousness

The sponsor posits that the incidence rates of insomnia and nervousness within the pool of studies 208, 209, and 367 are not high enough to warrant a special subsection in labeling; they provide the corresponding rates for Paxil and Zoloft, neither of which have precautions in labeling.

The Effexor XR rates, as well as odds ratios, are higher when calculated for the pool of studies 208 and 209, as proposed in our version of labeling (see Table 1). As will be discussed under **ADVERSE REACTIONS**, use of the pool of all short-term placebo-controlled studies (208, 209, and 367) appears to minimize the adverse event profile of Effexor XR compared to the pool of the two U.S. studies. Thus, it is recommended that the two-study pool be utilized and that this subsection be retained in labeling.

Table 1: A Comparison of the Incidence of Insomnia and Nervousness Between Two Study Pools

	208, 209, & 367			208 & 209		
	Eff %	Plac %	Odds Ratio	Eff %	Plac %	Odds Ratio
Insomnia	17%	11%	1.72	30%	14%	2.52
Nervousness	10%	5%	1.96	17%	6%	2.91

Changes in Appetite and Weight

Likewise, in the subsection describing changes in weight and appetite, the sponsor has used the three-study pool to present the incidence of treatment-emergent anorexia. The odds ratio for anorexia based on the two-study pool is higher than that for the three-study pool (3.63 vs. 2.25) so, again, use of the latter pool places Effexor XR in a more favorable light. It is recommended that this information be based on the two-study pool.

Activation of Mania/Hypomania

The sponsor proposes deletion of the term "activation" and the placebo rates as well as correction of the incidence in the Effexor (IR) premarketing trials. This is acceptable.

Seizures

Seizure incidence in the Effexor (IR) premarketing studies was adjusted to 0.26% from 0.3%. This is acceptable.

Use in Patients with Concomitant Illness

The sponsor has made several changes:

1) Information pertaining to the three patients with treatment-emergent QTc values over 500 msec has been deleted. They state that these values, reported in the original NDA submission, are in error based on the opinion of a panel of three cardiologists who manually measured the relevant ECG's under blinded conditions. These manual readings indicated that none of the QTc values exceeded 500 msec. This submission contained copies of the ECG tracings. Charles Ganley, M.D., a cardiologist in HFD-110, was informally consulted to read these tracings. He confirmed that none of the QTc values were over 500 msec.[1] Thus, this deletion is acceptable.

2) The sponsor argues that the mean increase in QTc among Effexor XR-treated patients (4.7 msec) is clinically insignificant given that the degree of variability in reading the QTc is generally higher than this change; providing this information is not useful or clinically relevant and may, in fact, be misleading. While it is true that a change of 4-5 msec in corrected QT for an individual patient is unlikely to have clinical importance given expected variation in this measure, a statistically significant difference in mean QTc between drug and placebo is worthy of mention in labeling since it may suggest a tendency toward clinically important QT prolongation under certain circumstances, such as overdosage.

3) Statements have been added to the effect that no clinically important ECG abnormalities were seen in Phase 2/3 studies with Effexor XR and that the incidence of treatment-emergent conduction abnormalities with Effexor (IR) was not different from placebo, consistent with Effexor labeling. This is not objectionable.

F. ADVERSE REACTIONS

The sponsor argues that the ADR tables should be based on the pool of the three short-term, placebo-controlled studies (208, 209, and 367) in lieu of the two U.S. studies (208 and 209), as we proposed. They provide a statistical analysis of a comparison of the

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[1]QTc values measured by Dr. Ganley versus the QTc originally reported are as follows: Patient #36505-101 = 457 vs. 572 msec, Patient # 36512-002 = 420 vs. 574 msec, and Patient # 36906-002 = 465 vs. 503 msec.

incidence of 11 common adverse events across the three studies.[2] This showed a significant difference in log odds ratio for only one adverse event, dry mouth. They also attest that safety data was collected reliably and consisently in all three studies.

However, it must be noted that such an analysis may be underpowered to detect important differences in adverse event incidence among the three studies. Perhaps a statistical comparison of the odds ratios between the two pools (i.e. studies 208, 209, and 367 versus 208 and 209) would be more useful but such an analysis was not done.

Nonetheless, a comparison of the impact of the two pooling strategies on prominent sections of labeling (e.g. adverse dropouts and common, drug-related events) may be a more critical issue. Table 2 compares the listing of adverse experiences that led to discontinuation[3] that would result from each pooling and the listing of common, probably drug-related events[4] that would follow from each pooling. Clearly, the listings are shorter if one uses the pool of the three studies and Effexor XR is placed in a more favorable light if this pool is used. While it could be debated that the shorter lists may be more "accurate," it could be argued with equal force that there is no evidence that this is the case. Also, the pool of the two domestic studies allows for a more conservative presentation of adverse event data in labeling and, since Effexor XR will be marketed in the U.S., the pool of the two U.S. studies may be more relevant. Hence, it is this reviewer's opinion that the core ADR information in labeling (i.e., table of adverse dropouts; 2% ADR table; and listing of common, drug-related adverse experiences) should focus on the pool of the two domestic studies as originally proposed.

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[2]The odds ratio for each event was calculated for each of the three studies. Then the natural logarithms of the odds ratios were tested for homogeneity using the Breslow-Day test.

[3]Those events leading to dropout in at least 1% of the Effexor XR patients and at a rate at least twice that of placebo.

[4]Those events occurring in at least 5% of the Effexor XR patients and at a rate at least twice that of placebo.

Table 2: Effect of Pooling Strategy on Adverse Event Listings in Effexor XR Labeling *		
Listing	Study Pool	
	208, 209, & 367 Neff = 357	208 & 209 Neff = 192
Common Adverse Events Leading to Discontinuation	Nausea Anorexia Dry Mouth **Dizziness** Insomnia **Somnolence**	Nausea Anorexia Dry Mouth Insomnia **Hypertension** **Diarrhea** **Paresthesia** **Tremor** **Blurred vision** **Delayed Ejaculation**
Common, Drug-Related Adverse Events	Abnormal ejaculation Nausea Dry Mouth Anorexia Dizziness Somnolence Abnormal dreams Sweating	Abnormal ejaculation Nausea Dry Mouth Anorexia Dizziness Somnolence Abnormal dreams Sweating **Abnormal orgasm** **Abnormal vision** **Constipation** **Flatulence** **Hypertension** **Impotence** **Insomnia** **Libido decreased** **Nervousness** **Tremor** **Vasodilatation** **Yawning**

* Bolded events are those not found in both lists within a pair.

Adaptation to Certain Adverse Events

The sponsor reinserted this statement after deletion from our proposal due to difficulty interpreting these data without a placebo control. It is recommended that it again be removed since our original reason for its deletion stands unchallenged.

Laboratory Changes

The sponsor proposes to remove the placebo mean change from baseline in cholesterol levels (a decrease of 7.4 mg/dL), contending that this mean decrease may be statistical artifact and its inclusion may be misleading. This may be true and I do not object to the omission of the placebo change from baseline; the small mean increase for the drug group (1.5 mg/dL) should be retained.

ECG Changes

A statistically significant difference between drug and placebo with respect to the mean change from baseline in QTc should be mentioned, if present. Data from the Effexor clinical trials has added; this is acceptable.

Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR

The sponsor has made several of the suggested changes to this subsection. However, since their **ADVERSE REACTIONS** section is based on the pool of studies 208, 209, and 367, a revision of the 2% ADR table based on the two-study pool (208 and 209) will necessitate modification of this listing.

G. DRUG ABUSE and DEPENDENCE

Physical and Psychological Dependence

The sponsor proposes to move information regarding discontinuation effects to the subsection **Discontinuing Effexor XR** under the **DOSAGE and ADMINISTRATION** to facilitate locating this information by clinicians. This proposal is satisfactory.

H. DOSAGE and ADMINISTRATION

Initial Treatment

The sponsor agrees with our conclusion that, for most patients, a starting dose of 75 mg/day is appropriate. However, they wish to add a statement indicating that it may be desirable to start at 37.5 mg/day in some patients to improve tolerability.

Additionally, they concede that the maximum recommended daily dose should be 225mg, based on available safety and efficacy data. They suggest titration to this dose, as needed, at intervals of not less than 4 days, with two-week incrementation intervals having been used in clincial trials.

The discussion of initial dosing is abbreviated but appears to contain the essential points of our proposal for this subsection.

These changes are acceptable.

However, language indicating that the minimum effective dose was 75 mg/day in the key efficacy trials should be modified since these trials were not designed to explore the smallest effective of Effexor XR in these patients. A statement indicating that 75 mg/day was the beginning dose is more accurate.

Discontinuing Effexor XR

Information regarding discontinuation symptoms has been moved from **DRUG ABUSE and DEPENDENCE** to this section as previously discussed.

III. Conclusions/Recommendations

It is recommended that the above changes be incorporated into final product labeling. A labeling draft including both changes and bracketed comments explicating these modifications has been prepared under separate cover.

Gregory M. Dubitsky, M.D.
August 13, 1997

cc: NDA #20,699
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

9-12-97

→ this NDA can now be approved S.e. mem. & file for more detailed response

→ Thomas P. Laughren, MD
TL, PDP

APPENDIX 1

STUDY 208: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D ANXIETY/SOMATIZATION FACTOR												
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN ER	92	7.14	92	-1.78	92	-3.10	92	-3.38	92	-3.55	92	-3.91
PLAC	99	7.14	99	-1.58	99	-2.35	99	-2.35	99	-2.33	99	-2.24
2-sided p-values for pairwise comparisons												
ER vs. P	-		0.50		0.02		0.001		<0.001		<0.001	
OBSERVED CASES ANALYSIS												
VEN ER	92	7.14	86	-1.79	78	-3.48	61	-3.91	62	-4.12	52	-4.62
PLAC	99	7.14	89	-1.73	75	-2.70	63	-2.63	57	-2.48	44	-2.76
2-Sided p-values for pairwise comparisons												
ER vs. P	-		0.84		0.02		<0.001		<0.001		<0.001	

APPENDIX 1

STUDY 208: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D COGNITIVE DISTURBANCE FACTOR												
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN ER	92	4.79	92	-1.93	92	-2.62	92	-2.99	92	-2.91	92	-3.18
PLAC	99	4.79	99	-1.22	99	-1.89	99	-1.85	99	-1.89	99	-2.04
2-sided p-values for pairwise comparisons												
ER vs. P	-		0.005		0.004		<0.001		<0.001		<0.001	
OBSERVED CASES ANALYSIS												
VEN ER	92	4.79	86	-2.00	78	-2.87	61	-3.27	62	-3.26	52	-3.59
PLAC	99	4.79	89	-1.35	75	-2.15	63	-1.98	57	-2.03	44	-2.63
2-Sided p-values for pairwise comparisons												
ER vs. P	-		0.01		0.01		<0.001		<0.001		0.01	

APPENDIX 1

STUDY 208: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D RETARDATION FACTOR												
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN ER	92	7.90	92	-2.37	92	-3.87	92	-4.56	92	-4.67	92	-5.25
PLAC	99	7.90	99	-1.62	99	-2.65	99	-2.89	99	-2.93	99	-2.76
2-sided p-values for pairwise comparisons												
ER vs. P	-		0.02		0.001		<0.001		<0.001		<0.001	
OBSERVED CASES ANALYSIS												
VEN ER	92	7.90	86	-2.30	78	-4.14	61	-4.98	62	-5.04	52	-5.92
PLAC	99	7.90	89	-1.74	75	-3.00	63	-3.24	57	-3.10	44	-3.43
2-Sided p-values for pairwise comparisons												
ER vs. P	-		0.09		0.005		<0.001		<0.001		<0.001	

APPENDIX 1

STUDY 208: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D PSYCHIC ANXIETY SCORE												
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN ER	92	2.28	92	-0.58	92	-1.18	92	-1.26	92	-1.28	92	-1.38
PLAC	99	2.28	99	-0.58	99	-0.72	99	-0.71	99	-0.77	99	-0.65
2-sided p-values for pairwise comparisons												
ER vs. P	-		0.99		<0.001		<0.001		<0.001		<0.001	
OBSERVED CASES ANALYSIS												
VEN ER	92	2.28	86	-0.57	78	-1.31	61	-1.43	62	-1.40	52	-1.48
PLAC	99	2.28	89	-0.64	75	-0.81	63	-0.85	57	-0.74	44	-0.79
2-Sided p-values for pairwise comparisons												
ER vs. P	-		0.59		<0.001		<0.001		<0.001		<0.001	

APPENDIX 1

STUDY 208: ADJUSTED MEAN CGI-IMPROVEMENT SCORES										
Treatment Group	Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
LAST OBSERVATION CARRIED FORWARD ANALYSIS										
VEN ER	92	2.89	92	2.23	92	2.07	92	1.99	92	1.82
PLAC	99	3.20	99	2.76	99	2.73	99	2.75	99	2.79
2-sided p-values for pairwise comparisons										
ER vs. P	0.03		<0.001		<0.001		<0.001		<0.001	
OBSERVED CASES ANALYSIS										
VEN ER	86	2.90	78	2.10	61	1.83	62	1.75	52	1.53
PLAC	89	3.12	75	2.61	63	2.57	57	2.61	44	2.30
2-Sided p-values for pairwise comparisons										
ER vs. P	0.14		0.001		<0.001		<0.001		<0.001	

APPENDIX 1

STUDY 209: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D ANXIETY/SOMATIZATION FACTOR										
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS										
VEN ER	91	6.90	91	-1.71	91	-2.38	91	-3.11	91	-3.13
PLAC	100	6.90	100	-1.49	100	-1.94	100	-2.21	100	-1.76
2-sided p-values for pairwise comparisons										
V vs. P	-		0.44		0.18		0.008		<0.001	
OBSERVED CASES ANALYSIS										
VEN ER	91	6.90	82	-1.86	78	-2.54	65	-3.66	60	-3.80
PLAC	100	6.90	93	-1.60	80	-2.21	62	-3.05	51	-2.34
2-Sided p-values for pairwise comparisons										
V vs. P	-		0.36		0.35		0.09		<0.001	

APPENDIX 1

STUDY 209: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D COGNITIVE DISTURBANCE FACTOR										
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS										
VEN ER	91	4.56	91	-1.55	91	-2.11	91	-2.36	91	-2.52
PLAC	100	4.56	100	-1.08	100	-1.43	100	-1.78	100	-1.64
2-sided p-values for pairwise comparisons										
V vs. P	-		0.06		0.009		0.02		0.001	
OBSERVED CASES ANALYSIS										
VEN ER	91	4.56	82	-1.50	78	-2.12	65	-2.51	60	-2.76
PLAC	100	4.56	93	-1.09	80	-1.59	62	-2.21	51	-2.04
2-Sided p-values for pairwise comparisons										
V vs. P	-		0.11		0.06		0.30		0.03	

APPENDIX 1

STUDY 209: ADJUSTED MEAN CHANGE FROM BASELINE IN HAM-D RETARDATION FACTOR										
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS										
VEN ER	91	8.15	91	-1.90	91	-2.99	91	-3.56	91	-4.07
PLAC	100	8.15	100	-1.70	100	-2.22	100	-2.73	100	-2.48
2-sided p-values for pairwise comparisons										
V vs. P	-		0.51		0.04		0.04		<0.001	
OBSERVED CASES ANALYSIS										
VEN ER	91	8.15	82	-1.92	78	-3.04	65	-3.89	60	-5.11
PLAC	100	8.15	93	-1.72	80	-2.46	62	-3.41	51	-3.57
2-Sided p-values for pairwise comparisons										
V vs. P	-		0.54		0.18		0.33		0.008	

APPENDIX 1

STUDY 209: ADJUSTED MEAN CHANGE FROM BASELINE IN PSYCHIC ANXIETY SCORE										
Treatment Group	Baseline		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS										
VEN ER	91	2.16	91	-0.64	91	-0.94	91	-1.08	91	-1.07
PLAC	100	2.16	100	-0.36	100	-0.59	100	-0.70	100	-0.55
2-sided p-values for pairwise comparisons										
V vs. P	-		0.01		0.005		0.004		<0.001	
OBSERVED CASES ANALYSIS										
VEN ER	91	2.16	82	-0.63	78	-0.94	65	-1.21	60	-1.22
PLAC	100	2.16	93	-0.35	80	-0.65	62	-0.92	51	-0.80
2-Sided p-values for pairwise comparisons										
V vs. P	-		0.01		0.03		0.06		0.01	

APPENDIX 1

STUDY 209: UNADJUSTED MEAN CGI-IMPROVEMENT SCORES								
Treatment Group	Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean
LAST OBSERVATION CARRIED FORWARD ANALYSIS								
VEN ER	91	3.03	91	2.71	91	2.45	91	2.29
PLAC	100	3.23	100	3.01	100	2.88	100	2.99
2-sided p-values for pairwise comparisons								
V vs. P	0.05		0.02		0.005		<0.001	
OBSERVED CASES ANALYSIS								
VEN ER	82	2.99	77	2.65	65	2.28	60	1.90
PLAC	93	3.24	80	2.86	62	2.52	51	2.57
2-Sided p-values for pairwise comparisons								
V vs. P	0.04		0.23		0.35		0.01	

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20-699
Sponsor:	Wyeth-Ayerst Research
Clock Date:	May 16, 1996

Drug Name

Generic Name:	Venlafaxine ER
Trade Name:	Effexor XR

Drug Categorization

Pharmacological Class:	Serotonin and norepinephrine reuptake inhibitor
Proposed Indication:	Depression Depression with associated anxiety Anxiety in depressed patients with associated anxiety
NDA Classification:	3 S
Dosage Forms:	37.5, 75, 100, 150 mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Completion Date:	February 26, 1997

TABLE OF CONTENTS

1.0 Materials Utilized in Review

1.1 Materials from NDA/IND

This clinical review entailed an examination of the following items:

NDA Volume(s)	Submission Date	Material
1.1	5/16/96	Table of contents, proposed labeling, summary of human pharmacokinetics
1.60	"	Table of studies
1.62	"	Study report: 600B-144-FR
1.63-1.72	"	Study report: 208
1.73-1.79	"	Study report: 209
1.80-1.84D	"	Study report: 367
1.85	"	Progress reports: studies 211 and 360
1.86-1.88	"	Interim report: 365
1.89-1.95	"	Interim report: 369
1.96	"	Progress reports: studies 101 and 210
1.97	"	Integrated summary of efficacy
1.98-1.1080	"	Integrated safety summary, COSTART glossary, drug abuse and overdose information
1.221-1.233	"	Index and case report forms for deaths and dropouts due to serious adverse events
3.1-3.2	9/18/96	Re-analysis of efficacy data for study 208 (excl. site #13), Phase 1 dose/duration table, line listing of TX-emergent adverse events
4.1-4.16	9/20/96	Index and case report forms for dropouts due to non-serious adverse events
*	9/27/96	Revised demographic and exposure tables
*	10/16/96	Supplemental efficacy data for study 208 (excl. site 20813) and for study 367

NDA Volume(s)	Submission Date	Material
6.1-6.7	11/7/96	Corrected volumes for 1.80, 1.81, 1.86, 1.87, 1.101, 1.103, and 1.108K
*	12/19/96	Identification of patients with PCS changes in labs, vital signs, and ECG's; revised tables of mean change from baseline in labs, vital signs, and ECG's
*	1/27/97	Corrected ECG data for patient 36728-002
*	2/13/97	Recalculated QTc statistics

* Volume number assignment pending.

Case report forms for the following patients (designated by study, site, patient #) were reviewed to audit the completeness and accuracy of data contained in the corresponding patient narrative summaries.

20814-029	20902-005	36503-011	36903-010
20818-009	20906-011	36505-301	36905-003
20820-002	20909-015	36509-005	36906-009
20821-008	20911-023	36712-002	36908-003
20822-031	20912-014	36713-102	

1.2 Related Reviews, Consults, etc.

The statistical review (dated 1/16/97), chemistry review (dated 1/17/97), pharmacology review (dated 2/5/97), and draft biopharmaceutics review (dated 2/18/97) for this NDA were examined.

2.0 Background

2.1 Indication

Venlafaxine HCl is a structurally novel antidepressant which was approved for marketing in the U.S. as Effexor on 12/28/93. Preclinical studies suggest that its mechanism of action is related to the inhibition of neuronal uptake of both serotonin and norepinephrine and, to a lesser degree, an inhibition of dopamine reuptake. Venlafaxine ER represents an extended release preparation of venlafaxine which can be taken on a simpler, once-a-day regimen compared to the BID or TID regimen for Effexor. The sponsor claims that venlafaxine ER is at least as effective as the marketed formulation and that nausea and the incidence of

sustained increases in blood pressure are reduced with venlafaxine ER compared to the marketed venlafaxine (IR). The sponsor proposes that venlafaxine ER (proprietary name: Effexor XR) be indicated for the treatment of depression, depression with associated anxiety, and the relief of anxiety in depressed patients with associated anxiety.

2.2 Important Information from Related IND's and NDA's and from Pharmacologically Related Agents

Related IND's and NDA's are as follows:

1)
2) NDA 20,151 for the approval of Effexor,
3)

Safety findings from the Effexor NDA revealed a few adverse effects associated with venlafaxine, which are not unexpected with drugs possessing sympathomimetic effects: elevations in blood pressure; decreases in weight and appetite; and CNS symptoms (anxiety, insomnia, nervousness). Otherwise, no particular toxicities have been associated with this compound.

2.3 Administrative History

An application to develop an sustained release formulation of venlafaxine was received by the Agency on 1/5/93 and assigned IND The 30-day SRD meeting was held on 2/1/93 and the sponsor was granted approval to proceed with 2 pilot studies. An End-of-Phase 2 meeting convened on 5/20/94; issues discussed with the firm included the following:

- the only Agency requirement for approval of an ER preparation of a marketed IR drug was bioequivalence for AUC (with 90% confidence) over the proposed dosage range. The sponsor indicated that they would conduct clinical efficacy trials nevertheless, to satisfy foreign marketing requirements.
- the sponsor asked if a demonstration of a superior adverse event profile for the ER vs. IR formulations could be labeled; we responded that this may be a possibility.
- the firm asked if approval of the IR formulation for other indications would be extended to the ER formulation; we stated that they would.
- no preclinical data was required as long as excipients, impurities, and metabolites were GRAS.

During a 10/3/95 teleconference with the firm, we granted approval to satisfy a Phase 4 commitment from the Effexor NDA (to

During the pre-NDA meeting on 11/21/95, the following issues were discussed:

- a statement in labeling regarding switching from the IR to the ER formulation could be based on bioequivalence for the major active metabolite, which is present in the circulation at a metabolite:parent ratio of 10:1.
- we requested submission of efficacy data in the form of our standard templates.
- we requested information showing the influence of dropouts on efficacy results.
- raw changes from baseline for efficacy measures were preferred as opposed to adjusted changes.
- biopharmaceutics requested dissolution data in 3 different media and suggested that the sponsor request a waiver for the 100mg capsule.

NDA 20,699 for the approval of venlafaxine ER was both submitted by the sponsor and received by Agency on May 16, 1996. The filing meeting was held on 6/28/96 and a decision was made to file this NDA.

2.4 Proposed Directions for Use

Directions for use conveyed in the sponsor's proposed labeling are as follows:

Effexor XR may be started at 37.5 mg/day for 7 days. For further clinical improvement, the dose may be increased by up to 75 mg/day to a maximum of 300 mg/day. Dose increments should be made at intervals of about 2 weeks or more, but not less than 4 days.

Effexor should be administered with food once daily, at about the same time either in the morning or in the evening. Capsules should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water.

Patients taking Effexor may be switched to Effexor XR at the nearest equivalent daily dose, e.g. Effexor 37.5mg BID to Effexor XR 75mg once daily.

The dosage should be reduced by 50% in patients with moderate hepatic impairment and by 25-50% in patients with renal impairment (GFR=10-70 mL/min); in patients undergoing hemodialysis, the total daily dose should be reduced by 50% and

be withheld until dialysis is completed (4 hrs).

No dosage adjustment is necessary for elderly patients, but extra care should be taken when increasing the dose in the elderly.

When discontinuing Effexor XR after more than 1 week of therapy, it is recommended that the dose be tapered.

2.5 Foreign Marketing

The immediate-release formulation of venlafaxine (venlafaxine IR) has been registered in over 30 countries with approvals pending in about countries at the time of NDA submission. It has been marketed in the U.S. since 1994 and in Europe since 1995, having been launched in the following countries:

Denmark	Netherlands
Germany	Spain
Greece	Sweden
Italy	United Kingdom

The ER formulation had not been marketed in any country

3.0 Chemistry

The chemistry reviewer (Maryla Guzewska, Ph.D.) has recommended that this NDA be given APPROVABLE status, subject to satisfactory inspection of the manufacturing facilities. Also, DMF's and are still pending review.

4.0 Animal Pharmacology

No preclinical data has been submitted to this NDA. The pharmacology reviewer has recommended two minor changes to the sponsor's proposed section in labeling on Mutagenicity, as described in his review.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

Seventeen studies in the venlafaxine ER development program were completed or were ongoing as of December 31, 1995. These are summarized individually in Appendix 5.1.1.1.

Four of these studies were ongoing at the time of the cutoff date for the NDA safety database and did not have interim safety analyses: 600B-211-US, 600B-360-CA, 600B-101-JA, and 600B-210-US. Studies 211 and 360 are Phase 3 studies in major depression. Study 101 is a Phase 1 trial and study 210 is a Phase 3 study in generalized anxiety disorder. Only serious adverse events from these studies are reported in the NDA submission, with a cutoff date of December 31, 1995.

An enumeration of all patients in the remaining 13 studies (8 Phase 1 and 5 Phase 3 studies) is shown in Table 5.1.1.1. Three of the Phase 3 studies were complete at the time of submission and have full study reports (600B-208-US, 600B-209-US, and 600B-367-EU). The other two Phase 3 studies (600B-365-EU and 600B-369-US) were ongoing but had interim safety reports with cutoff dates of August 31, 1995 (365) and September 30, 1995 (369). Also, for these two studies, information is provided for any serious, unexpected, and possibly drug-related study events which occurred from the interim report date to December 31, 1995; the interim data have not been integrated into the primary safety database.

5.1.2 Demographics

Demographic characteristics of all subjects in Phase 1 studies with venlafaxine ER are summarized in Table 5.1.2.1. Of these 144 subjects, most (131) received at least one dose of venlafaxine ER.

Demographic characteristics of subjects assigned to treatment with venlafaxine ER, placebo, or active comparator for Phase 3 studies are summarized in Table 5.1.2.2. Of the venlafaxine ER patients, roughly 10% were age 60 or older and the vast majority were Caucasian; males outnumbered females by a ratio of about 2:1.

Table 5.1.1.1: Patient Enumeration by Study Type					
Study Type	Ven ER	Ven IR	Other Ven *	Paroxetine	Plac
Phase 1 (Clinical Pharmacology)					
Single Dose	83	54	16	0	16
Multiple Dose	60	42	18	0	0
Subtotal	**143**	**96**	**34**	**0**	**16**
Phase 3 (Outpatient Studies in Depression)					
Acute, Placebo Controlled					
Flexible Dose	192	96	0	0	202
Fixed Dose	165	0	0	81	83
Uncontrolled					
Long-term	371	0	0	0	0
Subtotal **	**705**	**96**	**0**	**81**	**285**
Single-Dose Total	83	54	16	0	16
Multiple Dose Total	765	138	18	81	285
Grand Total	**848**	**192**	**34**	**81**	**301**

* Other venlafaxine includes intravenous venlafaxine and the GITS formulation of venlafaxine.
** Twenty-three patients received venlafaxine ER in both acute and long-term studies; they are counted only once in this subtotal.

Table 5.1.2.1: Demographic Characteristics of All Phase 1 Subjects (N=144)	
Age (years)	
Mean (SD)	27.34 (6.4)
Range	18-44
Sex N(%)	
Female	27 (18.7%)
Male	117 (81.3%)
Race N(%)	
White	105 (72.9%)
Non-white	39 (27.1%)
Height (in)	
Mean (SD)	69.71
Range	59.8-76.0
Weight (lb)	
Mean (SD)	164.36 (25.8)
Range	110.7-238.0

Table 5.1.2.2: Demographic Characteristics for Patients in Phase 3 Depression Studies				
	Ven ER (N=705)	Placebo (N=285)	Ven IR (N=96)	Paroxetine (N=81)
Age: <20	4 (0.6%)	1 (0.3%)	1 (1.0%)	0 (0.0%)
20-39	269 (38.2%)	130 (45.6%)	36 (37.5%)	23 (28.4%)
40-59	359 (50.9%)	135 (47.4%)	49 (51.1%)	44 (54.3%)
60-89	73 (10.3%)	19 (6.7%)	10 (10.4%)	14 (17.3%)
Age (years)				
Mean	43.61	41.86	42.48	48.26
Range	18-82	19-77	19-72	24-75
Sex				
Male	491 (69.6%)	177 (62.1%)	65 (67.7%)	44 (54.3%)
Female	214 (30.4%)	108 (37.9%)	31 (32.3%)	37 (45.7%)
Race				
White	679 (96.3%)	274 (96.1%)	86 (89.6%)	78 (96.3%)
Non-white	26 (3.7%)	11 (3.9%)	10 (10.4%)	3 (3.7%)
Weight (lb)				
Mean	162	166	171	157
Range	85-329	90-314	103-293	85-229

5.1.3 Extent of Exposure (dose/duration)

Duration of exposure and dose for those who received venlafaxine ER in these studies is profiled in Tables 5.1.3.1 for Phase 1 studies and in Table 5.1.3.2 for Phase 3 studies. Each subject or patient is enumerated according to mean daily dose and duration of exposure.

Among venlafaxine ER patients in Phase 3 studies, about 24% (169/705) were exposed to drug for 5½ months (165 days) or longer. However, only 9% (63/705) received a mean daily dose above 200 mg/day. A total of 8% (56/705) of the venlafaxine ER patients received a mean daily dose above 200 mg/day for durations longer than 5½ months.

Table 5.1.3.1:
Number (Percent) of all Subjects Receiving Venlafaxine ER According to Daily Dose and Duration of Therapy in Phase 1 Studies

Ven ER Exposure (Days)	Venlafaxine ER Dose		Total N (%)
	75 mg/day	150 mg/day	
1	17	1	18 (13.7%)
2	13	26	39 (29.8%)
3	14	0	14 (10.7%)
4	0	0	0 (0%)
5	18	0	18 (13.7%)
6	0	0	0 (0%)
7	0	0	0 (0%)
8	18	0	18 (13.7%)
9	0	0	0 (0%)
10	0	0	0 (0%)
11	0	0	0 (0%)
12	0	24	24 (18.3%)
Total N (%)	80 (61.1%)	51 (38.9%)	131 (100%)

Table 5.1.3.2: Number (Percent) of all Patients Receiving Venlafaxine ER According to Mean Daily Dose and Duration of Therapy in Phase 3 Studies

Duration (Days)	Mean Venlafaxine ER Dose (mg/day)					TOTAL	(%)
	0-50	51-100	101-200	201-300	>300		
1-7	3	21	7	0	0	31	(4.4)
8-14	3	8	2	0	0	13	(1.8)
15-21	6	22	4	0	0	32	(4.5)
22-28	0	12	11	0	0	23	(3.3)
29-44	1	11	15	0	0	27	(3.8)
45-104	0	101	217	1	0	319	(45.2)
105-164	0	40	45	6	0	91	(12.9)
165-224	0	38	52	17	1	108	(15.3)
225-284	0	5	12	18	5	40	(5.7)
285-344	0	0	5	11	2	18	(2.6)
>344	0	0	1	2	0	3	(0.4)
TOTAL	13	258	371	55	8	705	(100%)
(%)	(1.8)	(36.6)	(52.6)	(7.8)	(1.1)	100%	

The sponsor has proposed a maximum dose of Effexor XR 300 mg/day for general use. From the above table, it is seen that 55 patients were exposed to mean daily doses in the range 201-300 mg/day; however, it is not clear how these doses are distributed within that range, for example, how many patients were exposed to mean doses between 226 and 300 mg/day. Therefore, these data were refined to better evaluate the adequacy of exposure to doses above 225 mg/day.

Study 369, which was designed to assess long-term safety, was the only study in which doses above 225 mg/day were to be used, with a maximum daily dose of 375 mg/day. In this study, 47 patients received mean daily doses of venlafaxine ER (excluding missed doses) above 225 mg/day. Table 5.1.3.3 displays dose and exposure data for these 47 patients.

Table 5.1.3.3: Number of Patients Receiving a Mean Daily Dose of Venlafaxine ER >225 mg/day According to Mean Dose and Duration in Study 369					
Duration (Days)	Mean Venlafaxine ER Dose (mg/day)				TOTAL
	226-250	251-275	276-300	301-375	
91-180	6	1	2	0	9
181-270	8	6	6	6	26
271-360	2	5	2	3	12
TOTAL	16	12	10	9*	47

* This number is one greater than the number in the Table 5.1.3.2, probably because this table has excluded missed doses in calculating the mean daily dose.

Seventeen patients received mean doses in the range 276-375 mg/day for at least 6 months. In total, 38 patients received a mean daily dose in the range 226-300 mg/day, 29 of these for 6 months or longer. Also, 38 patients received mean doses greater than 225 mg/day for at least 6 months.

Person-time exposure to each treatment for the pool of integrated Phase 3 studies (208, 209, 365, 367, and 369), up to the primary safety cutoff dates, is as follows:

Treatment	N	Patient-Years
Venlafaxine ER	705	161.6
Placebo	285	42.4
Venlafaxine IR	96	16.4
Paroxetine	81	10.2

5.2 Secondary Source Data

5.2.1 Non-IND Studies

None.

5.2.2 Post-Marketing Experience

None.

5.2.3 Literature

As of April 1996, there was no published literature for

venlafaxine ER according to the sponsor. Results of study 208 were presented at the XIX CINP World Congress in Melbourne, Australia in June 1996, but these results have not been published.

5.3 Comment on Adequacy of Clinical Experience

Considerable post-marketing experience has accumulated with the immediate-release formulation of venlafaxine, without recognition of important safety problems which were not acknowledged at the time of Effexor approval. In this context, it is felt that this NDA contains sufficient information in terms of the demographic characteristics of the studied patients and duration of exposure to reasonably judge its efficacy and safety for marketing. If the maximum recommended dose is to be 225 mg/day, the above described exposure is felt to be adequate. If the sponsor's proposed maximum dose of 300 mg/day is to be instituted, the exposure to doses above 225 mg/day is considered to be marginally adequate (see Table 5.1.3.3).

5.4 Comment on Data Quality and Completeness

For nineteen patients selected at random (see section 1.1), case report forms (CRF's) were compared to the corresponding narrative summaries to assess the accuracy and completeness of data contained in the summaries. No deficiencies were found. Thus, the safety review relied primarily on narrative summaries in lieu of case report forms, which are more cumbersome to use.

The sponsor discovered some errors in data listings and supportive tables from studies 365 and 367 after submission of the NDA. On 11/7/96, seven volumes of corrected clinical data were received to replace volumes containing erroneous information.[1] Overall conclusions regarding safety and efficacy in these studies were not changed. Corrected data was used throughout this review.

One patient (36728-002) in the NDA database was noted to have experienced a markedly increased QTc per ECG. The CRF was requested for this patient to further explore this finding. Upon re-examination of the data for this patient, the sponsor discovered that the reported value was incorrect and forwarded corrected information in 1/27/97 and 2/13/97 submissions.

No other inadequacies in the quality of this data have been noted.

The principal investigator at site #13 of study 208 (Bruce

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[1] Volumes 1.80, 1.81, 1.86, 1.87, 1.101, 1.103, and 1.108K.

Diamond, Ph.D.) and one of his subinvestigators (Richard Borison, M.D.,Ph.D.) were indicted on 2/19/97 for diversion of research funds. According to correspondence from the sponsor dated September 18, 1996, this site was routinely monitored by Wyeth-Ayerst Research and, based on more than eight visits, it was concluded that the study performed by Dr. Diamond was in compliance with GCP. Nonetheless, since the efficacy data from this site was considered of uncertain reliability, the sponsor was requested to re-analyze data from that study, excluding this site. The revised data will be reviewed under section 7.2.1.1.

6.0 Human Pharmacokinetic Considerations

Previously reported pharmacokinetic information pertaining directly to the immediate-release formulation of venlafaxine is summarized in Effexor labeling and will not be repeated in this section, which will focus on findings in pharmacokinetic studies with venlafaxine ER and new information pertaining to the parent drug.

Based on single dose pharmacokinetic studies, the absolute bioavailability (PO/IV) of the venlafaxine ER formulation was about 40% and that for venlafaxine IR about 45%. Tmax after administration of the ER formulation was 6 hours for parent venlafaxine and 11 hours for the active ODV metabolite, which is the predominent circulating species.

The pivotal multiple dose bioequivalence study (study 136) was an open label, four-period, cross-over study of the relative bioavailability of 2 venlafaxine ER 75mg formulations given q24 hrs, 1 venlafaxine ER 150mg formulation q24 hrs, and the conventional formulation of venlafaxine 75mg q12 hrs in 12 healthy men and 12 healthy women. Dosing was conducted over 4 days per period. The 3 ER formulations produced lower steady-state venlafaxine Cmax and similar Cmin and AUC_{24h} compared to the conventional IR treatment. All 3 ER formulations produced steady-state ODV (O-desmethylvenlafaxine) Cmax, Cmin, and AUC_{24h} that were similar to those of the conventional formulation. There were no significant differences between men and women in the pharmacokinetic profile of venlafaxine ER.

In healthy volunteers, the administration of venlafaxine ER with food did not affect the absorption or disposition of either venlafaxine or ODV. The administration of a high fat meal with venlafaxine ER 150mg capsules did not produce a dose-dumping effect. Patients may take venlafaxine ER with or without meals.

A randomized, multiple-dose, crossover study comparing AM versus PM dosing with venlafaxine ER revealed no significant difference in the PK profiles, suggesting that patients may take their daily dose in the morning or the evening, provided it is taken at about the same time each day.

Although an in vitro metabolism study suggested that cytochrome P450 3A4 was involved in the metabolism of venlafaxine to N-desmethylvenlafaxine, this study was conducted with very high concentrations of the enantiomers and, thus, this study is not considered confirmatory.

An interaction study between venlafaxine and imipramine revealed no effect of imipramine on venlafaxine pharmacokinetics. Venlafaxine did not affect the pharmacokinetics of imipramine or 2-hydroxyimipramine. However, desipramine AUC, Cmax, and Cmin increased by 35% in the presence of venlafaxine. Also, 2-hydroxydesipramine AUC's were increased by 2.5-fold (with venlafaxine 37.5mg q12 hrs) and 4.5-fold (with venlafaxine 75mg q12 hrs). Past studies of the hydroxy metabolites of tricyclic antidepressants in animals suggested that these may possess cardiotoxic properties.[2] A survey of the literature produced three published studies which purportedly evaluated the potential ECG effects of 2-hydroxydesipramine.[3,4,5] The only clear finding was a strong correlation (r=0.86, p=0.002) between PR interval prolongation (mean change of 17 msec) and 2-hydroxydesipramine serum concentrations in 10 elderly depressed patients (Kutcher, et al); two of these patients developed first degree AV block but these changes were reportedly not closely related to steady state drug or metabolite concentrations. The clinical significance of this finding is not known.

A study of venlafaxine and ODV pharmacokinetics in poor and extensive cytochrome P450 2D6 metabolizers demonstrated higher parent drug concentrations in the PM's but similar exposure to the sum of (parent + ODV metabolite) between EM's and PM's.

The 75 and 150mg strengths of Effexor XR were used in bioavailability studies. A biowaiver can be granted for the 37.5 and 100mg strengths, which were not studied in vivo, on the basis of compositional proportionality, linear kinetics of venlafaxine and ODV to 450 mg/day, and comparable in vitro dissolution profiles to the studied strengths.

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[2] For example, see Pollock BG and Perel JM. Hydroxy metabolites of tricyclic antidepressants: evaluation of relative cardiotoxicity. In: Clinical Pharmacology in Psychiatry, ed. Dahl and Gram. Berlin, Germany:Springer-Verlag Press, pp. 232-236.

[3] Wilens TE, et al. J Am Acad Child Adolesc Psychiatry 1993; 32(4):798-804.

[4] Stern SL, et al. J Clin Psychopharmacol 1991;11:93-98.

[5] Kutcher SP, et al. Brit J Psychiatry 1986;148:676-679.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

This NA contains the results of three multicenter, randomized, double-blind, placebo-controlled, parallel group trials designed to evaluate the antidepressant efficacy of venlafaxine ER in outpatients with major depression:

- Study 208 was a 12-week U.S. flexible dose study in 293 patients which compared venlafaxine ER (75-150 mg/day) and venlafaxine IR (75-150 mg/day) to placebo.

- Study 209 was an 8-week U.S. flexible dose study in 197 patients that compared venlafaxine ER (75-225 mg/day) to placebo.

- Study 367 was a European study in 329 patients that compared two fixed doses of venlafaxine ER (75 and 150 mg/day) and paroxetine (20 mg/day) to placebo.

Two multicenter, randomized, double-blind, placebo-controlled, parallel group, flexible dose studies were in progress at the time of the NDA submission; progress reports for these two studies, which are still blinded, contain only data regarding serious adverse events:

- Study 211 is an 8-week U.S. study in about 300 patients with major depression which compares venlafaxine ER (75-225 mg/day) and fluoxetine (20-60 mg/day) to placebo.

- Study 360 is a 12 week Canadian study in about 330 patients which compares venlafaxine ER (75-225 mg/day) and fluoxetine (20-60 mg/day) to placebo in patients with major depression accompanied by anxiety.

Additionally, two ongoing, uncontrolled, open-label studies in depressed outpatients are described:

- Study 365 is a 12-month extension to Study 367 which evaluates the long-term safety of flexible dose venlafaxine ER (75-150 mg/day) in about 250 patients.

- Study 369 is a 12-month U.S. study of the long-term safety of flexible dose venlafaxine ER (75-375 mg/day) in about 120 patients.

Section 7.2.1 will focus on the three completed placebo-controlled studies (208, 209, and 367), since these are capable of providing persuasive evidence of clinical efficacy. Studies 211 and 360 were ongoing and still blinded at the time of submission and efficacy data are not available. Interim results of the two uncontrolled studies, which cannot provide convincing

evidence of efficacy, will be summarized in Section 7.2.2.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Controlled Studies

7.2.1.1 Study 208

Investigators/Locations

Principal investigators and study sites are identified in Appendix 7.2.1.1.

As discussed in section 5.4, efficacy data from site #13 was considered of questionable reliability. Thus, the sponsor was requested to reanalyze the efficacy results of this study, to exclude site 20813. The review of efficacy results is based on this reanalysis.

Objectives

The primary objective of this study was to compare the antidepressant efficacy and safety of venlafaxine ER with placebo.

Population

A total of 301 outpatients with DSM-III-R major depression were enrolled. Other inclusion criteria were:

- minimum age of 18 years.
- symptoms of depression for at least one month.
- minimum prestudy 21-item HAM-D total score of 20, with no greater than a 20% decrease between screening and study day -1.

Relevant exclusion criteria included the following:

- previous venlafaxine treatment.
- history or presence of any psychotic disorder not related to depression, bipolar disorder, or organic mental disorder.
- use of any investigational drug, antipsychotic drug, or ECT within 30 days; fluoxetine within 21 days; MAOI, paroxetine, or sertraline within 14 days; or any other antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic agent within 7 days (except chloral hydrate).
- use of any non-psychopharmacologic drug with psychotropic effects within 7 days of the study unless a stable dose had been maintained for the past month.
- drug or alcohol dependence within 1 year.

Also, the initiation or change in intensity of formal psychotherapy was prohibited during the study.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study conducted at 12 U.S. sites (including site 20813). Depressed patients with a HAM-D total score ≥20 underwent a single-blind placebo run-in for 7±3 days, during which they were evaluated for study eligibility. On study day -1, baseline safety and efficacy assessments were completed and patients who continued to meet selection criteria were randomized to begin either venlafaxine ER, venlafaxine IR, or placebo on day 1.

Treatment was continued for 12 weeks, followed by a tapering of medication for up to 2 weeks. Study visits were scheduled for days 7, 14, 21, 28, 42, 56, and 84; a post-study visit occurred 4-10 days after study medication had been discontinued. The HAM-D, MADRS, and CGI were performed at all visits through day 84 (week 12). An Investigator's and Patient's Subjective Rating as well as a Quality of Life Questionnaire were performed on day 84 (week 12).

A flexible dosing schedule was employed; total daily doses are depicted below for various time intervals during the study.

Period	Venlafaxine ER	Venlafaxine IR
Days 1-14	75mg	75mg
Days 15-84	75 or 150mg	75 or 150mg
Taper Wk 1	0 or 75mg	0 or 75mg
Taper Wk 2	0	0

Venlafaxine ER was administered as a single dose in the morning whereas venlafaxine IR was given BID. Doses could be increased to improve therapeutic response or reduced to improve tolerance within the ranges shown above. Patients unable to tolerate the minimum dose were to be discontinued from the study.

Analysis

The efficacy intent-to-treat (ITT) population included all enrolled patients who had at least a baseline measure on at least one primary efficacy parameter, took at least one dose of study medication, and had at least one evaluation on at least one primary efficacy measure either during treatment or within 3 days after the last dose. A total of XXX patients comprised the efficacy ITT.

This review focused on one-way analysis of variance (ANOVA), with therapy as the factor, for the pairwise comparisons of raw mean change from baseline at each visit in four key efficacy variables: HAM-D and MADRS total scores, HAM-D depressed mood item, and CGI-severity score. Analysis was performed on both observed cases (OC) and last-observation-carried-forward (LOCF) datasets. Statistical significance was defined at the $\alpha = 0.05$ level and all hypothesis testing was 2-sided.

Additionally, the sponsor discovered that the assumption of normality was not met for two variables: HAM-D depressed mood item and CGI-severity. Thus, non-parametric ANCOVA was applied to all key variables at each visit for the LOCF and OC datasets and the results of pairwise comparisons between venlafaxine ER and placebo based on ranks was provided.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.1. There were no remarkable differences between groups at baseline with respect to mean age, age range, gender composition, or the proportion of Caucasian patients.

Baseline Severity of Illness

There was no statistically significant difference among groups with respect to mean baseline HAM-D total scores, HAM-D depressed mood item scores, MADRS total scores, or CGI-severity scores.

Patient Disposition

Of the 270 patients randomized, 257 comprised the efficacy ITT, of which 85 were randomized to venlafaxine ER, 91 to placebo, and 81 to venlafaxine IR. The number of completers (i.e. patients with observed data for at least one of the four key efficacy variables), also expressed as a percentage of the efficacy ITT, at each visit is displayed in Appendix 7.2.1.1.

Of the ITT, 58% (49/85) of the venlafaxine ER, 47% (43/91) of the placebo, and 48% (39/81) of the venlafaxine IR patients completed 12 weeks of double-blind treatment; as expected, the most frequent reason for dropout among venlafaxine ER patients was an

adverse event (11% of the patients in the safety ITT), failure to return for follow-up among placebo patients (16%), and failure to return for follow-up among venlafaxine IR patients (15%).

Six patients dropped out due to a protocol violation:

- venlafaxine ER patient 20813-018 - took methamphetamine.
- venlafaxine ER patient 20819-004- elevated SGOT at screening; inadvertantly randomized.
- venlafaxine IR patient 20813-027 - scheduled too early for last visit.
- venlafaxine IR patient 20816-006 - noncompliant with study medication.
- placebo patient 20821-025 - failure to keep appointments and maintain consistent dosage.
- placebo patient 20821-031 - stopped study drug on own.

The visit at which at least 70% of the patients in both groups were still in-study and had observed efficacy data was week 4, with 86% of the venlafaxine ER, 77% of the placebo, and 83% of the venlafaxine IR patients remaining at that timepoint.

Dosing Information

The mean daily dose for all venlafaxine ER and venlafaxine IR patients at each visit is displayed in Appendix 7.2.1.1. Mean doses reached a plateau by week 4, with the mean venlafaxine ER dose slightly higher than the mean venlafaxine IR dose (135 vs. 123 mg/day).

Concomitant Medications

Of all study participants, most patients in each treatment group received a concomitant medication: venlafaxine ER 89%, placebo 86%, and venlafaxine IR 85%. The two most commonly used classes of concomitant agents were "anti-inflammatory/non-steroidal antirheumatics" and "other analgesics/antipyretics."

Four patients (1 venlafaxine ER and 3 placebo) received antidepressant medication with the study drug:

- placebo patient 20821-031 took Effexor 37.5mg bid beginning on day 8 and dropped out 4 days later.

- placebo patient 20822-030 took venlafaxine IR on days 2-4, then dropped out on day 6.

- placebo patient 20820-036 completed 12 weeks of treatment and started Effexor during the taper phase.

• venlafaxine ER patient 20822-003 took trazodone on day 5, then dropped out 2 days later due to insomnia.

Sedative-hypnotic agents were used by 4% of venlafaxine ER, 10% of placebo, and 10% of venlafaxine IR patients. Chloral hydrate up to 1000 mg at bedtime was permitted for sleep.

The only other psychotropic drug use was one venlafaxine ER patient, who used a psychostimulant, and one placebo patient, who used an anxiolytic drug. The details of this use were not located in the submission but this was not felt to play a significant role in the efficacy findings, particularly in light of the robustness of the results.

Overall, the above described concurrent use of psychotropic medication is not felt to have appreciably influenced the efficacy results of this study.

Efficacy Results

As noted previously, the following review is based on the efficacy reanalysis which excluded site 20813.

This review focused on the raw change from baseline for the four key efficacy variables: the HAM-D total score, HAM-D depressed mood item (item #1), MADRS total score, and the CGI-severity score. Efficacy analysis results are displayed for the LOCF and the OC datasets in Appendix 7.2.1.1.

Venlafaxine ER displayed consistent and highly significant superiority over placebo from week 4 onward for all four key variables in the LOCF analyses.

Similar results were observed from the OC analysis.

The results of non-parametric ANCOVA (including site 20813) likewise provide strong support of efficacy. (Data are displayed in vol. 1.66, pages 33-53).

The sponsor assessed for a treatment-by-center interaction across all study centers at each visit for all four key variables (both OC and LOCF datasets): there was no evidence of a consistent treatment-by-center interaction.

The sponsor also conducted a responder analysis, response being defined as a decrease of ≥50% from baseline in HAM-D total or MADRS total score or a CGI-improvement score of 1 (very much improved) or 2 (much improved). The proportions of efficacy ITT patients meeting response criteria were determined at each visit for both the LOCF and OC datasets. Statistical testing was done using the Fisher's exact test. Data from study week 6 onward are summarized below. This analysis corroborates the above findings.

	Ven ER	Placebo	p-value
HAM-D total (LOCF)			
Week 6	62%	35%	<0.001
Week 8	65%	36%	<0.001
Week 12	70%	32%	<0.001
HAM-D total (OC)			
Week 6	69%	38%	<0.001
Week 8	74%	39%	<0.001
Week 12	77%	48%	0.005
MADRS total (LOCF)			
Week 6	60%	31%	<0.001
Week 8	60%	31%	<0.001
Week 12	65%	27%	<0.001
MADRS total (OC)			
Week 6	67%	33%	<0.001
Week 8	68%	35%	<0.001
Week 12	75%	39%	<0.001
CGI-improvement (LOCF)			
Week 6	73%	42%	<0.001
Week 8	73%	38%	<0.001
Week 12	78%	37%	<0.001
CGI-improvement (OC)			
Week 6	82%	46%	<0.001
Week 8	84%	40%	<0.001
Week 12	88%	55%	<0.001

Conclusions

This study provides solid evidence of antidepressant efficacy.

7.2.1.2 Study 209

Investigators/Locations

Principal investigators and study sites are listed in Appendix 7.2.1.2.

Objectives

The study objective was to compare the antidepressant efficacy and safety of venlafaxine ER with placebo.

Population

A total of 204 outpatients with DSM-IV major depression were enrolled. Other inclusion criteria were:

- minimum age of 18 years.
- symptoms of depression for at least one month.
- minimum prestudy 21-item HAM-D total score of 20, with no greater than a 20% decrease between screening and study day -1.

Relevant exclusion criteria included the following:

- previous venlafaxine treatment.
- history or presence of any psychotic disorder not related to depression, bipolar disorder, or mental disorder due to a medical condition.
- use of any investigational drug, antipsychotic drug, or ECT within 30 days; fluoxetine within 21 days; MAOI within 14 days; or any antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic agent within 7 days (except chloral hydrate).
- use of any non-psychopharmacologic drug with psychotropic effects within 7 days of the study unless a stable dose had been maintained for the past month.
- drug or alcohol dependence within 1 year.

Also, the initiation or change in intensity of formal psychotherapy was prohibited during the study.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study conducted at 12 U.S. sites. Depressed patients with a HAM-D total score ≥20 underwent a single-blind placebo run-in for 7±3 days, during which they were evaluated for study eligibility. On study day -1, baseline safety and efficacy assessments were completed and patients who continued to meet selection criteria were randomized to begin either venlafaxine ER or placebo on day 1.

Double-blind treatment was continued for 8 weeks, followed by

medication tapering for up to 2 weeks. Study visits occurred on days 7, 14, 21, 28, 42, and 56; the HAM-D, MADRS, and CGI were administered at each visit. Also, an Investigator's and Patient's Subjective Rating was done on days 14, 21, and 56, and a Quality of Life Questionnaire was done on day 56.

A flexible dosing regimen was employed as shown below.

Period	Venlafaxine ER Dose
Days 1-14	75mg
Days 15-28	75 or 150mg
Days 29-56	75 or 150 or 225mg
Taper Wk 1	0 or 75 or 150mg
Taper Wk 2	0 or 75mg

Patients were instructed to take the study medication once daily in the morning. Doses were increased if clinically indicated to improve response. The dose could be reduced at any time to improve tolerance, with a minimum dose of 75mg after day 7.

Analysis

The efficacy intent-to-treat (ITT) population included all enrolled patients who had at least a baseline measure on at least one efficacy parameter, took at least one dose of study medication, and had at least one evaluation on at least one efficacy measure either during treatment or within 3 days after the last dose. A total of 191 patients comprised the efficacy ITT.

The efficacy analysis discussed below is based on an overall F-test, comparing the venlafaxine ER group with the placebo group, with respect to the raw mean change from baseline at each visit for four key efficacy variables: HAM-D and MADRS total scores, HAM-D depressed mood item, and CGI-severity score. Analysis was performed on both observed cases (OC) and last-observation-carried-forward (LOCF) datasets. Statistical significance was defined at the $\alpha = 0.05$ level and all hypothesis testing was 2-sided.

Additionally, since the assumption of normality for the HAM-D depressed mood item and CGI-severity was not met, the sponsor provided the results of a non-parametric ANCOVA for all key variables at each visit for both the LOCF and OC datasets.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.2. There were no statistically significant differences between groups at baseline with respect to age, sex, or race ($p = 0.26$, 0.50, and 0.68, respectively).

Baseline Severity of Illness

The difference in baseline HAM-D scores between groups approached statistical significance: mean score for venlafaxine ER= 24.53 and for placebo= 23.63, p= 0.07. However, the difference in baseline MADRS scores was not significant: venlafaxine ER mean= 27.99 and placebo mean= 27.75, p= 0.75.

Mean CGI-severity scores at baseline were roughly comparable; most patients in each group were rated as "mild" (64% of venlafaxine ER vs. 74% of placebo patients).

The relationship between baseline scores and outcome will be explored by the statistical reviewer.

Patient Disposition

Of the 204 patients enrolled, 197 were randomized and 191 comprised the efficacy ITT, of which 91 were randomized to venlafaxine ER and 100 to placebo. The number of completers (i.e. patients with observed data for at least one of the four key efficacy variables), also expressed as a percentage of the efficacy ITT, at each visit is displayed in Appendix 7.2.1.2.

Of the ITT, 66% (60/91) of the venlafaxine ER and 51% (51/100) of the placebo patients completed 8 weeks of double-blind treatment; as expected, the most frequent reason for dropout among venlafaxine ER patients was an adverse event (11% of the patients in the safety ITT) and the most frequent reason in the placebo group was lack of adequate response (22% of the safety ITT).

Three patients (2 venlafaxine ER and 1 placebo) dropped out for protocol violations:

- venlafaxine ER patient 20905-031 - discontinued study medication.
- venlafaxine ER patient 20910-007 - drug screen positive for drugs of exclusion.
- placebo patient 20906-014 - noncompliant with daily use of study medication.

The visit at which at least 70% of the patients in both groups were still in-study and had observed efficacy data was week 4, with 86% of the venlafaxine ER and 80% of the placebo patients remaining at that timepoint.

Dosing Information

The mean daily dose for all venlafaxine ER patients at each visit is displayed in Appendix 7.2.1.2. The mean dose appears to have reached a plateau at slightly over 170 mg/day during the last half of the study.

Concomitant Medications

Concomitant medication use was very common but generally similar between groups with respect to the proportion of patients taking given classes of agents. The most commonly used medications were analgesics/antipyretics (56% of both groups) and anti-inflammatory/non-steroidal antirheumatic agents (33% of venlafaxine ER and 43% of placebo patients).

It is notable that 3 venlafaxine ER and 3 placebo patients received an antidepressant drug during the study. Of the 3 venlafaxine ER patients, 2 (20901-027 and 20902-002) dropped out on days 35 and 28, respectively, due to inadequate therapeutic response; they were prescribed the antidepressants (venlafaxine IR and sertraline, respectively) during the taper periods. The third patient (20901-020) completed the study but was started on venlafaxine IR during the taper period. Similarly, the 3 placebo patients dropped out due to lack of efficacy and took antidepressant medication during the taper period. Given that none of these 3 patients took an antidepressant during the critical 8 week period for evaluating efficacy, this use should not affect the efficacy results of the study.

Efficacy Results

This review focused on the raw change from baseline for the four key efficacy variables: the HAM-D total score, HAM-D depressed mood item (item #1), MADRS total score, and CGI-severity score. Efficacy analysis results are displayed for the OC and LOCF datasets in Appendix 7.2.1.2.

The LOCF analyses demonstrate consistent and statistically significant superiority of venlafaxine ER over placebo for all 4 variables at the end of weeks 4, 6, and 8; this difference was highly significant at the end of week 8 ($p < 0.001$).

For the OC analyses, findings were not consistent over these visits. Differences were significant at the end of week 4, except for the MADRS total score which was in the trend range ($p=0.08$). This was followed, at the end of week 6, by a sizable decrease in both sample sizes, continued overall improvement in both groups, and loss of statistical significance despite numerical superiority of drug over placebo. Then at the end of week 8, there was further attrition in both groups but more so in the placebo group; venlafaxine ER patients showed further overall improvement while the placebo patients did not improve, restoring statistical superiority to the drug.

The results of the non-parametric, rank-based comparisons of venlafaxine ER and placebo similarly support the efficacy of venlafaxine ER; as with the parametric analyses, the OC results were not as consistent over time as the LOCF results. These data

are displayed in vol. 1.75, pages 25-46.

The sponsor assessed for a treatment-by-center interaction across all study centers at each visit for all four key variables (both OC and LOCF datasets): there was no evidence of a consistent treatment-by-center interaction.

The sponsor also conducted a responder analysis, response being defined as a decrease of ≥50% from baseline in HAM-D total or MADRS total score or a CGI-improvement score of 1 (very much improved) or 2 (much improved). The proportions of efficacy ITT patients meeting response criteria were determined at each visit for both the LOCF and OC datasets. Statistical testing was done using the Fisher's exact test. Statistically significant differences are summarized below.

	Ven ER	Placebo	p-value
HAM-D total (LOCF)			
Week 6	49%	34%	0.04
Week 8	58%	29%	<0.001
HAM-D total (OC)			
Week 8	73%	45%	0.003
MADRS total (LOCF)			
Week 8	48%	28%	0.005
MADRS total (OC)			
Week 8	63%	43%	0.04
CGI-improvement (LOCF)			
Week 6	58%	42%	0.03
Week 8	60%	37%	0.001
CGI-improvement (OC)			
Week 8	73%	55%	0.05

Conclusions

The LOCF analysis provides strong evidence of antidepressant efficacy from Week 4 onward. The OC analysis, while not as strong probably as a result of both attrition and placebo response, also is considered to support the LOCF results. Finally, the responder analysis shows clear differences between drug and placebo at the end of weeks 6 and 8. Overall, this study provides solid evidence of antidepressant efficacy for venlafaxine ER.

7.2.1.3 Study 367

Investigators/Locations

Principal investigators and locations of these foreign study sites are listed in Appendix 7.2.1.3.

Objectives

The primary objective of this study was to compare the safety and efficacy of two fixed doses of venlafaxine ER (75 and 150 mg/day) to placebo in depressed outpatients.

Population

A total of 332 outpatients with DSM-III-R major depression were enrolled. Other inclusion criteria included:

- minimum age of 18 years.
- symptoms of depression for at least one month.
- minimum prestudy 21-item HAM-D total score of 20, with no greater than a 20% decrease between screening and baseline visits.

Relevant exclusion criteria included the following:

- history or presence of any psychotic disorder not related to depression, bipolar disorder, or organic mental disorder.
- use of any investigational drug, antipsychotic drug, or ECT within 30 days; fluoxetine within 21 days; MAOI, paroxetine, or sertraline within 14 days; or any other antidepressant, anxiolytic, sedative-hypnotic, or other psychotropic agent within 7 days (except chloral hydrate).
- use of any drug with psychotropic effects within 7 days of the study unless a stable dose had been maintained for the past month.
- drug or alcohol dependence within 1 year.

Design

This was a randomized, double-blind, placebo- and active-controlled, double-dummy, parallel group, fixed dose study conducted at 35 sites in Europe. After a 7-10 day single-blind placebo run-in, which was intended to exclude early placebo responders, eligible patients were randomized to one of four treatment arms: venlafaxine ER 75 mg/day, venlafaxine ER 150 mg/day, placebo, or paroxetine 20 mg/day.

Double-blind treatment at the assigned fixed dose was continued for 8 weeks. Dosing during all 8 weeks was constant, with no titration to the assigned fixed dose. Patients took all study medication in the morning given as three capsules, two peach-

colored and one blue-colored: peach capsules contained venlafaxine ER 75mg or placebo and blue capsules contained paroxetine 20mg or placebo (double-dummy design). Any patient intolerant of the assigned dose was dropped out.

During a subsequent 3 day taper period, all patients received placebo except for patients who had taken venlafaxine ER 150mg, who received venlafaxine ER 75mg during taper.

Study visits occurred at the end of weeks 1, 2, 4, 6, and 8 during double-blind treatment. Primary efficacy assessments were performed at each visit and consisted of the HAM-D, MADRS, and CGI.

Analysis

The efficacy intent-to-treat (ITT) population included all patients who had been enrolled in double-blind therapy, had a baseline evaluation on at least one primary variable (HAM-D, MADRS, or CGI), took at least one dose of assigned medication, and had at least one evaluation on one of the primary variables either during therapy or within 3 days of last treatment. A total of 323 patients comprised the efficacy ITT.

This review focused on a one-way analysis of variance (ANOVA), with therapy as the factor, for the pairwise comparisons of raw mean change from baseline at each visit in four key efficacy variables: HAM-D and MADRS total scores, HAM-D depressed mood item, and CGI-severity score. Analysis was performed on both observed cases (OC) and last-observation-carried-forward (LOCF) datasets. Statistical significance was defined at the $\alpha = 0.05$ level and all hypothesis testing was 2-sided. Although it could be argued that the α level should be adjusted for multiple comparisons, given comparisons of the two venlafaxine ER groups versus placebo, it is clear from examination of the efficacy results (see below) that such adjustment would not change the overall efficacy conclusion from this study.

For purposes of analysis, the 35 study sites were pooled to combine data from sites with small sample sizes; this resulted in 9 centers. This pooling, which was determined prior to breaking the blind, is depicted in vol. 1.80 on page 20.

Baseline Demographics

Baseline demographic data is displayed by treatment group in Appendix 7.2.1.3. There was no statistically significant difference among groups with respect to age, sex, or race ($p = 0.14$, 0.20, and 0.54, respectively).

Baseline Severity of Illness

There were no statistically significant differences between groups with respect to baseline HAM-D total scores, HAM-D depressed mood item scores, MADRS total scores, or CGI-severity scores.

A large majority of patients in each group were rated at baseline as either "moderately ill" or "markedly ill" on the CGI-severity item: 79% of venlafaxine ER 75mg, 79% of venlafaxine ER 150mg, 81% of placebo, and 86% of paroxetine patients.

Patient Disposition

Of the 332 patients enrolled, 329 were randomized and 323 comprised the efficacy ITT, of which 83 were randomized to venlafaxine ER 75mg, 78 to 150mg, 82 to placebo, and 80 to paroxetine. The number of completers (i.e. patients with observed data for at least one of the four key efficacy variables), also expressed as a percentage of the efficacy ITT, at each visit is displayed in Appendix 7.2.1.3.

The percentages of patients who completed 8 weeks of double-blind treatment in each group is as follows:

Venlafaxine ER 75mg	64% (53/83)
Venlafaxine ER 150mg	62% (48/78)
Placebo	65% (53/82)
Paroxetine	60% (48/80)

The most frequent reason for dropout in each treatment group (% of the safety ITT) is as follows: inadequate response in the 75mg patients (7%), an adverse event in the 150mg patients (12%), inadequate response in the placebo group (16%) and inadequate response in the paroxetine group (16%).

Two paroxetine patients were withdrawn for protocol violations:

- patient 36729-016 - intake of alprazolam.
- patient 36739-003 - high transaminase value at baseline.

The visit at which at least two-thirds of the patients in both groups were still in-study and had observed efficacy data was week 6, with 70% of the 75mg group, 69% of the 150mg group, 70% of the placebo group, and 69% of the paroxetine group remaining at that timepoint.

Concomitant Medications

More than 50% of patients in each group received concomitant medication during the study. By far, the most commonly used drug class (between 40-45% of patients in each group) was "psycholeptics:" this consisted almost entirely of chloral hydrate and zolpidem; these drugs were permitted for sleep by

protocol. "Psychoanaleptics" (not defined by the sponsor) were used by 1% of placebo and 4% of paroxetine patients. It is not felt that the above concomitant drug use substantially influenced the study efficacy results.

Efficacy Results

This review focused on the raw change from baseline for the four key efficacy variables: the HAM-D total score, HAM-D depressed mood item (item #1), MADRS total score, and the CGI-severity score. Efficacy analysis results are displayed for the OC and the LOCF datasets in Appendix 7.2.1.3.

There were no consistent patterns of statistically significant differences between either venlafaxine ER group and placebo for any of the four key variables for either the LOCF or OC analyses, even without adjustment for multiple comparisons. There was one isolated significant difference: at the final visit, the 75mg group was superior to placebo for the observed cases dataset (p= 0.03).

There were no statistically significant differences between paroxetine and placebo at any timepoint, for any key variable, for either dataset in this study.

The sponsor assessed for a treatment-by-center interaction at each visit for the following measures: HAM-D total score, MADRS total score, and CGI improvement score (LOCF dataset): overall, there was no evidence of a consistent treatment-by-center interaction. However, the statistical reviewer did note that two sites (36717 and 36722) were atypical in that there was a 100% response rate with respect to the HAM-D total score (see below) across all treatment groups at these sites (combined N=27).

A responder analysis, with response defined as a ≥50% decrease from baseline in HAM-D or MADRS total scores or a CGI-improvement score of "much improved" or "very much improved," revealed no statistically significant differences for the overall comparisons of the proportions of responders among the four treatment groups.

Conclusions

Study 367 provided no persuasive evidence of antidepressant efficacy for venlafaxine ER. Comparison of week 8 change from baseline data for the key variables from this study with the corresponding data from studies 208 and 209 reveals the following patterns:

- the mean changes from baseline for the venlafaxine ER groups in 367 are generally greater than those of 208 and 209.

- the mean changes from baseline for the placebo group in 367 are generally greater, often considerably so, than those of 208 and 209.
- the absolute difference between the mean venlafaxine ER and placebo changes from baseline are generally considerably less in 367 compared to those in 208 and 209.

From these observations, it seems that a major reason for the lack of drug-placebo differences in this study is the large placebo response.

It is notable that paroxetine, which is a widely recognized antidepressant agent, also failed to demonstrate superiority over placebo. Of course, this begs the question of whether 20mg can be considered an effective dose in these patients; current labeling recommends antidepressant doses in the range 20-50 mg/day for most patients. In fact, several of the mean changes for placebo surpassed those of paroxetine, suggesting that paroxetine had a minimal effect for many of these patients, inconsistent with its reputation as an established antidepressant. The question of how many of these paroxetine patients would have responded at higher doses must remain unanswered. Nonetheless, since 20mg is deemed to be in the effective dose range, it is assumed that there existed poor assay sensitivity in this study and this study is considered failed.

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7.2.2 Other Trials Pertinent to the Efficacy Evaluation

As noted mentioned in the overview to the efficacy section, there are two long-term, open label, uncontrolled studies of venlafaxine ER in depressed outpatients: studies 365 and 369. Interim reports, to include interim efficacy data, for these studies were included in the original submission and will be summarized below.

Study 365 was a six month study, with the possibility of six additional months of treatment if clinically indicated, which was conducted at 37 European centers. Patients who completed study 367 and were in need of further antidepressant treatment could be enrolled; however, other patients with DSM-III-R major depression could be enrolled as well. The cutoff date for the interim report was August 31, 1995. Efficacy variables included the HAM-D total score and CGI-severity score. In the LOCF analysis (N=244), the mean raw changes from baseline in the HAM-D total score from months 4 to 10 were consistently in the range of -10 to -11, with 95% CI's of about -9 to -12. There was substantial attrition after month 4 but, up to that timepoint, OC results were similar. CGI-severity score raw changes from baseline from months 4 to 10 were in the range -1.6 to -1.8 (95% CI's about -1.4 to -2.0) in the LOCF analysis. At month 4, OC results were similar. The sponsor reports a significant therapy-by-center interaction in this study: at some centers, there was no significant change from baseline while substantial improvement was noted at other sites. This was attributed by the sponsor to wide differences at baseline in illness severity. The sponsor also performed a responder analysis, with response defined as a decrease in HAM-D total score of at least 50% OR a CGI-improvement score of "1" (very much improved) or "2" (much improved). In the LOCF dataset, at least 45% of patients met response criteria on visits at months 2, 4, and 6, with slightly higher corresponding rates in the OC dataset.

Study 369 was a six month study, with the possibility of six additional months of treatment if clinically warranted, which was conducted at 10 U.S. sites. The cutoff date for the interim report was September 30, 1995. The primary objective of this study was to collect long-term safety data; therefore, only limited efficacy data are available. Efficacy assessment was based on CGI scores. LOCF mean changes from baseline for the CGI-severity score (N=111) were in the range -1.35 (month 2) to -1.92 (month 6); for the OC analysis, mean changes were slightly higher, probably as a result of selection bias during the course of the study. The sponsor also performed a responder analysis, with response defined as a CGI-improvement score of "1" (very much improved) or "2" (much improved). In the LOCF dataset, at least two-thirds (67%) of patients met response criteria on visits at months 2, 3, 4, 5, and 6, with similar results in the OC dataset.

Efficacy results from these uncontrolled studies cannot provide persuasive evidence of efficacy but do suggest the hypothesis that venlafaxine ER has long-term efficacy. This hypothesis should be tested using an appropriately designed trial (e.g. a relapse prevention study).

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

Subset analyses based on age (<60 or ≥60), sex (male or female), and baseline HAM-D score (<27 or ≥27) were performed for the pool of studies 208 and 209.[1] An analysis based on race was not considered due to the small number of patients in non-white ethnic groups in these two studies.

The adjusted mean change from baseline in HAM-D total score at week 8 for venlafaxine ER patients under 60 (N=176) was -12.6 versus -10.4 for those 60 and older (N=7); mean changes in the placebo subgroups were -8.1 (N=187) and -8.0 (N=12), respectively. This difference in means is not felt to be clinically remarkable. However, given the relatively small number of older patients, this data must be interpreted with caution; no statistical testing was done by the sponsor.

In this pool of studies, females outnumbered males almost 2:1 in the venlafaxine ER, venlafaxine IR, and placebo treatment groups. For the gender subgroups, analysis of the adjusted mean changes from baseline to week 8 for the LOCF datasets with respect to the HAM-D total score, HAM-D depressed mood item, MADRS total score, and CGI-severity score across the three treatment groups revealed no consistently significant gender effects (α=0.10).

About two-thirds of the patients in each of the three treatment groups in this study pool had less severe depression (HAM-D score <27) at baseline. Baseline severity subgroup analysis was performed with respect to the HAM-D total score, HAM-D depressed mood item, MADRS total score, and CGI-severity score. For each severity subset, there was consistent statistical superiority of venlafaxine ER over placebo at weeks 4, 6, and 8 for all variables. However, for the venlafaxine ER patients, the adjusted mean changes from baseline at week 8 were numerically greater for patients with more severe depression versus less severe depression at baseline.

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[1]The poolability of the three efficacy trials (208, 209, and 367) was tested using the Inverse-Chi-Square method for the HAM-D total scores at week 8: the combined null hypothesis of no significant protocol effect with respect to treatment differences was rejected.

Overall, there was no evidence to suggest a significant effect of age, sex, or baseline illness severity on therapeutic outcome.

No information was provided to support a plasma concentration-response relationship for venlafaxine ER.

7.3.2 Size of Treatment Effect

It is difficult to characterize the treatment effect size for an antidepressant agent. Additionally, any comparison of treatment effects across studies must be interpreted with a huge grain of salt, given the multiplicity of potential confounding variables. With this in mind, the placebo-adjusted effect sizes[2] on each of the four key variables at week 6 from the observed cases analysis are depicted in Table 7.3.2 below for:

- study 208 (venlafaxine ER and IR),
- study 301 (the most robust flexible dose efficacy study in the original venlafaxine NDA 20,151, using a dose range of 75-225 mg/day), and
- study 003-022 (the strongest flexible dose efficacy study in NDA 20,415 for mirtazepine, the most recently approved antidepressant).

All drug-placebo differences were statistically significant (α= 0.05). All studies used the 21-item version of the HAM-D.

Table 7.3.2:
Placebo-Adjusted Mean Changes from Baseline at Week 6 (OC) in Flexible Dose Antidepressant Trials

	208		301	003-022
	Ven ER	Ven IR	Ven IR	Mirtazepine
HAM-D total	-4.6	-3.8	-6.0	-8.4
HAM-D item #1	-0.9	-0.8	-0.7	-0.7
MADRS total	-5.5	-5.3	-7.2	-9.2
CGI-severity	-0.6	-0.5	-0.7	-1.1

The results from study 209 are not displayed in this table because, at week 6, venlafaxine ER/placebo differences were not statistically significant; however, at week 8, venlafaxine ER was statistically superior, with effect sizes roughly comparable to

[2]Scores = (mean drug change from baseline) minus (mean placebo change from baseline). Thus, negative numbers imply drug superiority over placebo.

those in study 208: HAM-D total= -5.1, HAM-D item #1= -0.7, MADRS total= -5.9, and CGI-severity= -0.7.

Probably the most reliable comparison is between venlafaxine ER and IR within study 208, since these two treatment groups can be assumed to be reasonably balanced with respect to potential confounders. From this comparison, it is seen that the mean effect sizes for venlafaxine ER are slightly higher than those for venlafaxine IR, an approved antidepressant.

7.3.3 Choice of Dose

Data from study 367, the fixed dose trial, did not provide solid evidence of efficacy for either the 75mg or 150mg dose of venlafaxine. Thus, an evaluation of dose-response from this study is not feasible. Dose-response cannot be reliably assessed in flexible dose trials.

The sponsor proposes to indicate in labeling that the usual therapeutic dose of Effexor XR is 75 mg/day and that, for further clinical effect, the dose may be increased to a maximum of 300 mg/day.

In support, the sponsor provides the results of an analysis of those patients from the pool of the two positive studies (208 and 209) who remained at 75 mg/day (i.e. those for whom dose increases were not deemed to be necessary to improve efficacy): this subset comprised 43% (79/183) of the venlafaxine patients. A comparison group was the placebo patients in this pool who did not require an increase in the number of study capsules. Pairwise comparisons of mean change from baseline in the four key variables at weeks 2, 3, 4, 6, and 8 between these two subsets revealed statistically significant superiority of venlafaxine ER over placebo (LOCF dataset). A similar analysis using those patients who required an increase in study medication dose did not indicate consistent statistical superiority for venlafaxine ER until week 8. Additionally, a responder analysis based on CGI-improvement scores utilizing these same subgroups of venlafaxine ER and placebo patients revealed clear superiority ($p \leq 0.001$) of drug at week 8 (LOCF).

It is reasonable to ask whether those patients who required a dose increase above 75mg experienced an enhanced therapeutic effect compared to those who remained at the low dose: an examination of placebo-adjusted response rates at week 8 indicates a slightly higher response rate among patients who needed no dose increase (approximately 35% vs. 25%); this finding is supported by larger placebo-adjusted mean changes from baseline in HAM-D total and CGI-severity scores among low dose patients (-6.2 vs. -3.7 and -1 vs. -0.6, respectively). Thus, the sponsor concludes that the 75mg dose is effective for a large portion of depressed patients and these patients tend to

experience improvement in depression similar to that observed in patients who require a dose increase.

It must be commented that the 75mg patients do not represent a randomized sample but rather a group selected on the basis of response to that dose; it is likely that patients who are relatively treatment-resistant are overrepresented in the group that required dose escalation to either 150mg or 225mg. Thus, efficacy comparisons between the low and higher dose patients must be viewed skeptically. Nonetheless, assuming that 1) these patients, as a whole, reasonably represent the general target population with respect to therapeutic responsiveness and 2) the flexible dosing used in these trials reflect how venlafaxine ER is likely to be used in clinical practice, it is reasonable to conclude that a large proportion of patients will respond to a 75 mg/day dose. Both assumptions are plausible.

The proposed maximum dose is 300 mg/day. However, the maximum daily dose studied in the clinical efficacy trials was 225 mg/day (study 209). The mean doses were about 138 mg/day and 176 mg/day in studies 208 and 209, respectively. It was considered that the higher proposed maximum dose may be based on extrapolation from the efficacy database for Effexor (NDA 20,151).

Two Effexor trials demonstrated efficacy at doses above 225 mg/day: a flexible dose study (206) in depressed, melancholic inpatients using a mean dose of about 350 mg/day (max. 375 mg/day) and a fixed dose study (203) in depressed outpatients, which showed superiority over placebo for 75, 225, and 375 mg/day but without evidence that the highest dose had any advantage over the two lower doses. Given the increased risk of hypertension with higher doses, it was felt that there would be no benefit, but increased risk, to use a dose higher than 225 mg/day in most patients. Therefore, Effexor labeling indicates no evidence of usefulness of doses greater than 225 mg/day for moderately depressed patients but adds that severely depressed inpatients responded to a mean dose of 350 mg/day; in the latter group, doses up to 375 mg/day may be helpful, generally in three divided doses.

This fails to explain why an Effexor XR dose up to 300 mg/day should be proposed for general use. In the absence of a compelling rationale for using a higher maximum dose, it is recommended that a maximum dose of 225 mg/day be labeled.

Finally, it is not clear why a starting dose of 37.5 mg/day was chosen. In the three controlled trials with Effexor XR, venlafaxine was started at doses of 75 mg/day (208, 209, and low dose patients in 367) and 150 mg/day (high dose patients in 367). It does not appear that these starting doses were poorly tolerated and there does not appear to be any advantage to delaying titration to the usual therapeutic dose. Thus, a

starting dose for most patients should be the usual therapeutic dose, 75 mg/day.

7.3.4 Duration of Treatment

The effectiveness of venlafaxine ER for more than 12 weeks has not been systematically evaluated in controlled studies.

7.4 Conclusions Regarding Efficacy

Table 7.4 summarizes the efficacy results for the three controlled efficacy trials at week 4, the timepoint at which at least 70% of the ITT sample for each treatment group remained in study.

These data, in conjunction with the more detailed efficacy data displayed in the Appendices and discussed previously, clearly show a significant drug effect favoring venlafaxine ER over placebo in studies 208 and 209.

No effect was evident in study 367, even without adjustment of the alpha level due to placebo comparisons with two dose groups. Since no effect was observed for the active comparator, paroxetine, this study is best considered failed, probably in large part due to a substantial placebo response.

Considering these studies as a whole, it is concluded that convincing evidence of antidepressant activity for venlafaxine ER has been demonstrated.

Table 7.4
Summary of Efficacy Results for Key Variables
(Significance of Drug/Placebo Comparisons for Mean Change from Baseline at Week 4)[3]

Study	Treatment Group	HAM-D total		HAM-D item #1		MADRS total		CGI-severity	
		LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
208	VEN ER	**	*	**	**	**	**	**	**
	VEN IR	tr	tr	**	**	*	*	ns	ns
209	VEN ER	**	*	**	*	*	tr	**	*
367	VEN ER 75	ns	ns	ns	ns	ns	ns	ns	tr
	VEN ER 150	ns	ns	ns	ns	ns	ns	ns	ns
	PAROXETINE	ns	ns	ns	ns	ns	ns	ns	ns

[3]Significance Codes: ns= not significant (p>0.10)
tr= trend (0.05<p≤0.10)
*= significant (0.01<p≤0.05)
**= highly significant (p≤0.01)

Datasets: LOCF= Last Observation Carried Forward, OC= Observed Cases

8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The evaluation of the safety of venlafaxine ER in the treatment of depression consisted of two general approaches:

1) an examination of the entire Phase 1/Phase 3 venlafaxine ER clinical trials database (Nven= 848) for more serious adverse events, specifically deaths (section 8.1.1), dropouts (8.1.2), and other serious adverse events (8.1.3);

2) an examination of less serious safety findings within selected pools of controlled studies from the integrated safety database, specifically adverse events (8.1.5), laboratory findings (8.1.6), vital signs (8.1.7), and ECG's (8.1.8). In addition, the following safety areas are surveyed: emergent suicidality (8.1.4), withdrawal phenomena and abuse potential (8.1.10), human reproductive data (8.1.11), and human overdose experience (8.1.12).

Please note that, in the eight Phase 1 studies, there were no serious adverse events and no dropouts due to adverse experiences. Also, among the four ongoing studies without interim safety analyses (studies 101, 210, 211, and 360), no serious adverse events were reported as of the 12/31/95 cutoff date. Hence, the following safety review focuses exclusively on five Phase 3 studies: the three short-term, placebo-controlled trials (208, 209, and 367) and the two long-term studies with interim safety reports (365 and 369). The Phase 3 integrated database comprises studies 208, 209, 367, 365 (to 8/31/95), and 369 (to 9/30/95). For studies 365 and 369, this review included only serious adverse events from these cutoff dates to the extended cutoff date of 12/31/95.

Important findings from the above review processes are organized into a review of systems (8.2), followed by a summary of the key safety findings (8.3).

The cutoff date for safety data in the integrated summary of safety was September 30, 1995, for non-European studies and August 31, 1995, for European studies. For studies 365 and 369, information was also provided for any serious, unexpected, and possibly drug-related study events from these dates through December 31, 1995. Only serious events from the four studies which were not integrated were reported (see section 5.1).

The numbers of patients at-risk and person-time exposure for each treatment group in the pool of Phase 3 studies (208, 209, 365, 367, and 369), up to the cutoff date, is as follows:

Treatment	N	Patient-Years
Venlafaxine ER	705	161.6
Placebo	285	42.4
Venlafaxine IR	96	16.4
Paroxetine	81	10.2

8.1.1 Deaths

One patient in the integrated safety database died during a clinical trial: 36713-102 (secondary to injuries from a suicide attempt by hanging). This case will be discussed under the review of systems (section 8.2.6.3.1).

This case yields a mortality rate of 0.62 per 100 PEY's (crude rate= 0.14%).

Additionally, two patients died during ongoing studies after the cutoff date for the integrated safety database: 36514-002 (pulmonary embolism) and 36524-009 (acute pulmonary edema). These cases will be discussed under the review of systems (sections 8.2.3.3.1 and 8.2.1.3.1, respectively).

None of these deaths can be reasonably attributed to treatment with venlafaxine ER.

There were no deaths in Phase 1 studies.

8.1.2 Dropouts

8.1.2.1 Overall Pattern of Dropouts

In the integrated Phase 1 studies, only three subjects prematurely discontinued study participation: one at the subject's request because of poor sleep at the study site, one due to a positive urine screen for cocaine, and one for an upper respiratory infection.

Table 8.1.2.1 enumerates venlafaxine ER dropouts in the integrated Phase 3 study pool, as well as venlafaxine ER and placebo dropouts in the pool of placebo-controlled studies (208, 209, and 367), according to the primary reason for dropout as indicated by the investigator.

The most common reason for dropout among venlafaxine ER patients was an adverse event (12%). The modal reason in the placebo group was lack of efficacy (16%).

The sponsor was queried regarding the classification of study

events as "adverse experiences," "other medical events," or "other non-medical events" since the algorithm for this classification was unclear from the submission. In an 11/8/96 telecon with Kenneth Bonk (W-A Regulatory Affairs), it was clarified that this classification was solely at the discretion of the individual investigator and that no specific guidance for classifying events was provided by the company.

There were three dropouts in Phase 1 studies, for the following reasons: subject's request, protocol violation (+urine test for cocaine), and other medical reason (upper respiratory infection deemed not related to study drug).

Table 8.1.2.1:
Number (%) of Dropouts by Primary Reason for Dropout

	Placebo-Controlled Studies		Phase 3
	Venlafaxine ER N=357	Placebo N=285	Venlafaxine ER N=705
Lack of Efficacy	22 (6)	47 (16)	47 (7)
Adverse Event	36 (10)	11 (4)	88 (12)
Failed to Return	25 (7)	26 (9)	38 (5)
Patient Request	5 (1)	10 (4)	19 (3)
Protocol Violation	4 (1)	3 (1)	8 (1)
Other Medical Event	3 (1)	4 (1)	13 (2)
Other Non-Medical Event	5 (1)	5 (2)	14 (2)
TOTAL	100 (28%)	106 (37%)	227 (32%)

8.1.2.2 Adverse Events Associated with Dropout

For all premature discontinuations, the investigators were required to indicate the primary reason for dropout and, if applicable, any secondary reasons. Table 8.1.2.2 depicts the adverse events which were listed as primary or secondary reasons for premature discontinuation in at least 1% of either venlafaxine ER group and the proportions of each group dropping

out with that adverse event. Nausea was the adverse event most commonly associated with venlafaxine ER patient dropout in both study pools.

There were no dropouts for an adverse event in Phase 1 studies.

Table 8.1.2.2:
Number (%) of Dropouts with Adverse Events

	Placebo-Controlled Studies		Phase 3
	Venlafaxine ER N=357	Placebo N=285	Venlafaxine ER N=705
Body as Whole			
Headache	3 (<1)	3 (1)	12 (2)
Asthenia	4 (1)	3 (1)	7 (<1)
Digestive			
Nausea	13 (4)	1 (<1)	26 (4)
Vomiting	3 (<1)	0 (0)	9 (1)
Anorexia	4 (1)	1 (<1)	7 (<1)
Dry Mouth	4 (1)	0 (0)	4 (<1)
Nervous			
Dizziness	8 (2)	3 (1)	12 (2)
Somnolence	6 (2)	2 (<1)	12 (2)
Insomnia	5 (1)	1 (<1)	6 (<1)

8.1.3 Other Serious Adverse Events

The Wyeth-Ayerst medical monitor reviewed all study events to identify those which were serious. This identification was based on three criteria:

- the regulatory definition of serious events (i.e. fatal, life-threatening, permanently disabling, requiring inpatient hospitalization, congenital anomalies, cancers, or overdoses).

- the sponsor's in-house designation of certain events as potentially serious (i.e. pregnancies, seizures, suicide attempts, symptomatic arrhythmias, and liver function test elevations).

• the investigator's assessment of the clinical significance of study-emergent events.

Within the context of these criteria, the medical monitor evaluated all available and solicited data to make a judgement regarding event classification as serious versus non-serious.

During the course of examining individual patient data as part of this review, it was not obvious to this reviewer why a particular event had been classified as serious in some cases. Nonetheless, all events considered serious by the sponsor are discussed as serious events in this review.

Serious adverse events will be discussed under the appropriate section of the Review of Systems (section 8.2). Suicide attempts and overdoses will be addressed in sections 8.1.4.1 and 8.1.12, respectively.

8.1.4 Other Search Strategies

Special searches were conducted to determine the relative incidence of: 1) events related to the emergence of suicidality; 2) events that might represent the emergence of hostility, overt aggression, or violent behavior; and 3) possible allergic skin reactions. These searches and the results will be presented under the appropriate review of systems subsections (sections 8.2.6.3.1, 8.2.6.3.3, and 8.2.8.3.2, respectively).

8.1.5 Adverse Event Incidence Tables

8.1.5.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

Treatment-emergent study events were defined as all adverse events that were not seen before the first study drug intake or that worsened during treatment.

The sponsor classified verbatim adverse event terms using a standard COSTART thesaurus (5th edition). A glossary of the COSTART terms and the subsumed verbatim terms (located in volume 1.98, pages 183-223) was examined to evaluate the appropriateness of this coding. In general, this classification seemed reasonable. However, three findings were noted:

1) "Abnormal liver function tests," "SGOT increased," and "SGPT increased" are three separate COSTART terms in this glossary: it may be appropriate to subsume these under a common term.

2) "Abnormal ejaculation/orgasm" and "anorgasmia" are two separate COSTART terms in the glossary; both terms include events experienced by patients of either gender. Abnormal orgasm and anorgasmia likely reflect a disturbance in the same physiological

process and thus should be combined. Also, it may be useful to make "abnormal ejaculation" a distinct term, since ejaculation and orgasm are different events, and to stratify "abnormal orgasm" by gender.

3) "Abnormal vision" and "Abnormal accomodation" are two separate COSTART terms. Given that the vast majority of events coded as abnormal vision represent the verbatim term "blurred vision" and that the events coded as abnormal accomodation represent "difficulty focusing eyes," it would be appropriate to combine these terms since the latter events are likely to manifest as blurred vision.

The effects of venlafaxine ER on liver enzymes will be addressed more objectively by examination of laboratory data and, thus, the coding of these adverse events is not a critical issue.

To address the second issue, the submitted ADR incidence data has been modified by this reviewer to reflect the combined incidence of "abnormal orgasm" and "anorgasmia" under the term "abnormal orgasm" and to indicate the total incidence by gender (i.e. abnormal orgasm (males) and abnormal orgasm (females)) in the 1% ADR table appended to this review (Appendix 8.1.5.2.1). Additionally, the incidence of "abnormal ejaculation" is listed separately.

Similarly, the COSTART terms "Abnormal vision" and "Abnormal accomodation" will be combined as abnormal vision in the appended 1% ADR table.

Additionally, a number of COSTART terms were felt to be poorly suited to convey meaningful information in labeling (e.g. abnormal thinking). The corresponding verbatim terms were examined and were used to provide clarifying footnotes in the appended ADR table.

8.1.5.2 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

The adverse event table provided in the Integrated Safety Summary displays the proportions of patients experiencing specific events within the pool of the short-term depression studies 208, 209, and 367. Since these three studies differ with respect to a number of variables, as summarized in Table 8.1.5.2 below, the task of determining an appropriate study population for examination of adverse events is complicated. In addition, the incidence of many adverse events in the European study seemed to be substantially lower than in the two domestic studies.

It seemed that the most appropriate approach would be to examine the pool of the two US studies, 208 and 209. Appendix 8.1.5.2.1. displays the proportions of patients in the venlafaxine ER and

placebo treatment groups from this pool who experienced adverse events that were reported in at least 1% of the venlafaxine ER group.

Table 8.1.5.2:
Summary of Short-term Depression Study Characteristics

Study	Location	Dosing Regimen	Doses (mg/day)	Duration (weeks)	N(venER)
208	US	Flex	75-150	12	97
209	US	Flex	75-225	8	95
367	Europe	Fixed	75,150	8	83(75mg) 82(150mg)

Appendix 8.1.5.2.2 displays the categorical incidence of adverse events which were reported in venlafaxine ER patients within the pool of all venlafaxine ER Phase 3 studies (N=705) except for those events noted in Appendix 8.1.5.2.1.

8.1.5.3 Identifying Common and Drug-Related Adverse Events

Treatment-emergent adverse events that are considered common and drug-related (i.e. reported in at least 5% of venlafaxine ER patients at an incidence at least twice that in the placebo group), based on data from the 1% ADR table (Appendix 8.1.5.2.1), are shown in Table 8.1.5.3.

Table 8.1.5.3:
Common and Drug-Related Treatment-Emergent Adverse Events:
Pool of Studies 208 and 209

	% Reporting Event	
	Ven ER (N=192)	Placebo (N=202)
Cardiovascular System		
Vasodilatation[1]	6%	1%
Hypertension	5%	<1%
Digestive System		
Nausea	41%	14%
Dry Mouth	17%	8%
Constipation	14%	6%

Anorexia	13%	4%
Flatulence	8%	4%
Nervous System		
Dizziness	30%	11%
Insomnia	30%	14%
Somnolence	24%	10%
Nervousness	17%	6%
Abnormal Dreams[2]	11%	3%
Tremor	6%	1%
Libido Decreased	5%	<1%
Respiratory System		
Yawn	5%	0%
Skin		
Sweating	16%	3%
Special Senses		
Abnormal Vision[3]	8%	<1%
Urogenital System		
Abnormal Ejaculation[4,5]	24%	0%
Impotence[5]	7%	1%
Abnormal Orgasm (Female)[6,7]	6%	<1%
Abnormal Orgasm (Male)[5,8]	6%	1%

[1] Mostly "hot flashes."
[2] Mostly vivid dreams, nightmares, and increased dreaming.
[3] Mostly "blurred vision" and "difficulty focusing eyes."
[4] Mostly "delayed ejaculation."
[5] Incidence is based on the number of male patients.
[6] Mostly "delayed orgasm" or "anorgasmia."
[7] Incidence is based on the number of female patients.
[8] Mostly "delayed orgasm."

Events for which the venlafaxine ER incidence was higher than the placebo incidence by a statistically significant degree (α=0.100) will be discussed under the appropriate subsection of the review of systems (8.2). Please note that all proportions were analyzed using a 2-tailed Fisher's exact test.

Adverse events identified as being common and drug-related in the clinical review of NDA 20,151 for the approved, immediate-release venlafaxine were: abnormal ejaculation/orgasm, anorexia, anxiety, asthenia, blurred vision, constipation, dizziness, dry mouth, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

8.1.5.4 Additional Analyses and Explorations

8.1.5.4.1 Dose-Relatedness

Only data from the fixed dose study (367) is potentially useful in addressing the dose-relatedness of certain adverse events. However, even this data does not provide a convincing evaluation of the effect of dose on event occurrence, since only two dose levels were studied.

Nonetheless, the incidence rates of treatment emergent adverse events by dose for this study were examined to detect those events for which there was some evidence of increasing incidence with increasing dose. The criterion used to discern dose relatedness in this review was arbitrarily chosen to be as follows: an incidence in the 150 mg/day group which is at least 3% higher and 1½ times the 75 mg/day incidence. The events meeting this criterion are listed in Table 8.1.5.4.1.

Table 8.1.5.4.1:
Incidence of Dose Related Adverse Events
(Study 367)

	Ven ER 75 mg/day	Ven ER 150 mg/day
Pain	1%	4%
Palpitations	0%	4%
Constipation	1%	4%
Nausea	16%	23%
Depression	1%	4%
Sweating	10%	15%
Urinary retention	0%	4%
Abnormal ejaculation	0%	7%

8.1.5.4.2 Adaptation to Drug Over Time

The sponsor performed an analysis of the incidence of certain study events over time (8 weeks) which examined cohorts of completers on venlafaxine ER who experienced an event during the first week of treatment. For this analysis, studies 208, 209, and 367 were pooled. Results are shown in Table 8.1.5.4.2 below.

Table 8.1.5.4.2:
Incidence (%) of Adverse Events over 8 Weeks Among Venlafaxine ER Completers with the Event at Week 1

	Week #							
	1	2	3	4	5	6	7	8
Anorexia	100	56	33	22	0	0	0	0
Constipation	100	71	57	57	57	43	43	29
Dizziness	100	25	17	17	8	0	0	0
Insomnia	100	94	65	47	35	18	18	18
Nausea	100	44	17	10	4	4	4	0
Nervousness	100	67	50	33	25	25	25	8
Somnolence	100	65	48	30	26	26	26	22
Sweating	100	82	73	73	64	45	36	18

There is some evidence of adaptation for several of these events, but particularly for dizziness and nausea (week one N= 12 and 52, respectively). However, the interpretation of these results is difficult given the lack of comparison to a placebo control, where the degree of spontaneous adverse event resolution could be estimated.

8.1.5.4.3 Adverse Event/Demographic Interaction

The sponsor examined the relationship between the occurrence of certain adverse events (dizziness, insomnia, nausea, and somnolence) and demographic characteristics (age and gender); the effect of race on event occurrence was not examined due to the relatively small numbers of non-white study participants. The pool of studies 208, 209, and 367 was examined.

Patients <65 years old were compared with those ≥65: odds ratios were not significantly different (α= 0.10; Breslow-Day test).

Likewise, a comparison of odds ratios between males and females indicated no effect of gender on event occurrence.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing

Laboratory testing in the primary integrated database consisted of clinical chemistry, hematology, and urinalysis. The laboratory analyses performed for each specific study and their frequency is shown in Appendix 8.1.6.1. These batteries of tests are adequate to study the effects of Venlafaxine ER on common laboratory variables.

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The pool of studies 208, 209, and 367 was chosen as the primary database to evaluate the effects of venlafaxine ER on laboratory variables relative to placebo. Although these studies varied somewhat with respect to design characteristics, this pool was felt to be reasonably homogeneous for the purpose of evaluating laboratory test changes. Examination of dropouts due to laboratory abnormalities, however, was conducted across the entire Phase 3 integrated safety database (i.e. studies 208, 209, and 367 as well as the long-term, uncontrolled studies 365 and 369) and for the 8 studies in the Phase 1 integrated database.

Standard analyses consisted of the following:

1) a comparison of mean changes from baseline to final on-drug assessment between venlafaxine ER and placebo treatment groups.
2) a comparison of the proportions of patients meeting criteria for significant abnormalities in laboratory parameters between drug and placebo treatment groups.
3) an comparison of the proportions of patients dropping out for laboratory abnormalities between drug and placebo.

8.1.6.3 Standard Analyses and Exploration of Laboratory Data

8.1.6.3.1 Analyses Focused on Measures of Central Tendency

A summary of mean change from baseline to last on-drug visit for each clinical chemistry analyte is presented in Appendix 8.1.6.3.1.1.

Measures of mean change from baseline for a number of chemistry analytes showed some statistically significant differences when compared to placebo (sodium, chloride, BUN, alkaline phosphatase, cholesterol, uric acid, total protein, and albumin). These will be discussed under the review of systems.

A summary of mean change from baseline for each hematology analyte is presented in Appendix 8.1.6.3.1.2. Small statistically (but not clinically) significant decreases in

hemoglobin and hematocrit were observed from baseline. These changes were slightly greater for the placebo group as compared with the venlafaxine ER group.

A summary of mean change from baseline for urinalysis measures is presented in Table 8.1.6.3.1.3. No statistically significant changes were seen.

8.1.6.3.2 Analyses Focused on Outliers

Criteria for identifying patients with potentially clinically significant (PCS) changes in laboratory parameters are listed in Appendices 8.1.6.3.2.1 (chemistry), 8.1.6.3.2.2 (hematology), and 8.1.6.3.2.3 (urinalysis).

The proportions of patients meeting these criteria are displayed in Appendices 8.1.6.3.2.4, 8.1.6.3.2.5, and 8.1.6.3.2.6, respectively. Note that the Phase 3 denominators, which were used to compute Phase 3 rates in the right column of each table, were not corrected for venlafaxine ER patients who participated in both short- and long-term studies; corrected fractions would be slightly higher.

In general, the venlafaxine ER incidence was comparable to or less than the corresponding placebo rate for PCS lab values. Important findings will be discussed under the review of systems.

8.1.6.3.3 Dropouts for Laboratory Abnormalities

One venlafaxine ER patient (20821-004) and no placebo patients discontinued the study because of abnormal laboratory test results. This case (hypokalemia and albuminuria) will be discussed under the review of systems.

8.1.6.4 Additional Analyses and Explorations

None.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Measurement in the Development program

Appendix 8.1.7.1 depicts the vital sign assessments and frequencies of assessment for all five studies in the integrated safety database. These are felt to be adequate to reasonably evaluate the effects of venlafaxine ER on vital signs.

8.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The pool of studies 208, 209, and 367 was chosen as the primary database to evaluate the effects of venlafaxine ER on vital sign parameters relative to placebo. Although these studies varied somewhat with respect to design characteristics, as discussed in section 8.1.5.2, this pool was felt to be reasonably homogeneous for the purpose of evaluating vital sign changes. Examination of dropouts due to vital sign abnormalities, however, was conducted across the entire Phase 3 integrated safety database (i.e. studies 208, 209, and 367 as well as the long-term, uncontrolled studies 365 and 369) and for the 8 studies in the Phase 1 integrated database.

Most analyses pertinent to changes in blood pressure focused on the measurements of supine diastolic blood pressure (SDBP), since this was deemed by the sponsor to be the most clinically relevant blood pressure parameter and it is the major parameter of interest in current Effexor labeling.

Standard analyses consisted of the following:

1) a comparison of mean changes from baseline between venlafaxine ER and placebo treatment groups.
2) a comparison of the proportions of patients meeting criteria for significant abnormalities in vital sign parameters between drug and placebo treatment groups.
3) an comparison of the proportions of patients dropping out for vital sign abnormalities between drug and placebo.

8.1.7.3 Standard Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Analysis Focused on Measures of Central Tendency

Appendix 8.1.7.3.1 depicts mean changes from baseline for vital sign measures within the pool of short-term, placebo-controlled studies.

Although the actual mean changes from baseline among venlafaxine ER patients were small in size, there were statistically significant mean increases in most blood pressure measures in the venlafaxine ER group versus placebo.

Also, there was a statistically significant difference in mean weight change, with a overall decrease in the venlafaxine ER group compared to placebo (-1.151 versus +1.020 lbs, $p<0.001$).

These findings will be discussed further in the review of systems (section 8.2).

8.1.7.3.2 Analyses Focused on Outliers

Appendix 8.1.7.3.2.1 lists the criteria used by the sponsor to identify vital sign and weight changes of potential clinical significance.

Appendix 8.1.7.3.2.2 displays the proportions of patients who had at least one measurement during therapy defined as significant by these criteria. This analysis entailed venlafaxine ER and placebo patients within the pool of short-term, placebo-controlled studies as well as venlafaxine patients in the total Phase 3 integrated database.

There were statistically significant differences[1] between venlafaxine ER and placebo for the following variables, with a higher proportion of drug patients with abnormal values compared to placebo: elevated diastolic blood pressure, decreased diastolic blood pressure with postural change, and increased weight. These findings will be discussed in the review of systems.

8.1.7.3.3 Dropouts for Vital Sign Abnormalities

A total 9 venlafaxine ER and one placebo patient dropped out due to abnormalities in vital signs or weight in the five Phase 3 studies in the integrated safety database. These dropouts are enumerated by reason for dropout in Table 8.1.7.3.3.1 below.

Table 8.1.7.3.3.1:
Enumeration of Premature Discontinuations due to Vital Sign or Weight Changes

	VEN ER (N=705)	PLACEBO (N=285)
Elevated blood pressure	5 (0.7%)	1 (0.4%)
Tachycardia	1 (0.1%)	0
Weight gain	2 (0.3%)	0
Weight loss	1 (0.1%)	0

Dropouts will be discussed further in the review of systems (section 8.2).

[1]Two-tailed Fisher's exact test.

8.1.7.4 Additional Analyses and Explorations

The sponsor conducted analyses to: 1) examine the effect of baseline blood pressure on blood pressure changes, 2) assess the incidence of sustained increases in blood pressure, and 3) explore the dose-relatedness of blood pressure changes. The results of these analyses will be described in the review of systems.

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