8.1.8 ECG's

8.1.8.1 Extent of ECG Recording in the Development Program

Appendix 8.1.8.1 depicts the frequency of standard 12-lead electrocardiogram assessments for the five studies in the integrated safety database. These evaluations are felt to be adequate to reasonably evaluate the effects of venlafaxine ER on ECG parameters.

8.1.8.2 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 ECG parameters relative to placebo. Although these studies varied somewhat with respect to design characteristics, this pool was felt to be reasonable for the purpose of evaluating ECG changes. Examination of dropouts due to ECG abnormalities was conducted across the entire Phase 3 integrated safety database (i.e. studies 208, 209, 367, 365, and 369) and for the 8 Phase 1 studies.

8.1.8.3 Standard Analyses and Explorations of ECG Data

Standard analyses consisted of the following:

1) a comparison of mean changes from baseline between venlafaxine ER and placebo.
2) a comparison of the proportions of patients meeting criteria for significant abnormalities in ECG measures for drug versus placebo.
3) an comparison of the proportions of patients dropping out for ECG abnormalities between drug and placebo.

8.1.8.3.1 Analyses Focused on Measures of Central Tendency

Mean ECG changes from baseline final visit on drug for the short-term, placebo-controlled study pool are presented in Appendix 8.1.8.3.1. The mean changes were generally small and not considered to be clinically significant. The mean increase in heart rate of approximately 4 beats/min while on venlafaxine ER was statistically significant compared to placebo. Also, the mean increase in QTc for venlafaxine ER was statistically different from placebo. These findings will be further discussed in section 8.2.

8.1.8.3.2 Analyses Focused on Outliers

Individual ECG results were first screened against criteria specified by tne Wyeth-Ayerst medical monitor to identify those ECG parameters that exceeded the reference intervals (Appendix

8.1.8.3.2.1) and therefore, were considered potentially clinically significant.

The proportion of patients with potentially clinically significant changes during phase III studies are shown in Appendix 8.1.8.3.2.2. Results are shown only for venlafaxine ER and placebo treated patients. In the table, the total number of patients refers to the number of patients who were evaluated for a particular variable.

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.

The incidence of potentially clinically significant increases in the QTc interval was significantly higher in the venlafaxine ER groups than in the placebo group (p=0.026, 2-tailed Fishers Exact test).

This finding will be further discussed in the review of systems.

The incidences of potentially clinically significant changes in the other ECG variables were similar to those for the placebo group.

8.1.8.3.3 Dropouts for ECG Abnormalities

There is no significant difference in dropout rates for ECG abnormalities among Phase 3 venlafaxine ER and placebo patients: Three venlafaxine ER patients and no placebo patients dropped out due to ECG abnormalities (0.4% vs. 0.0%; p=0.561).

The case summaries of ECG dropouts[1] were reviewed and will be discussed under the review of systems.

8.1.8.4 Additional Analyses and Explorations

None.

8.1.9 Special Studies

Study 600B-144-FR studied primarily the absolute single dose bioavailability of venlafaxine ER 75mg capsules and a conventional formulation (CF) of venlafaxine 50mg capsules in 16 healthy adult subjects using a cross-over design. Secondary objectives were to compare the EEG effects and visual analog

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[1]Patients 36902-006, 36905-004, and 36906-002.

ratings for nausea for these formulations.

There were no deaths or serious adverse events in this study.

Pharmacokinetic results are discussed in section 6.0.

The principle EEG effect of venlafaxine, regardless of formulation, was an increase in fast β energy (20-30 Hz) as well as reduction in α energy, which were more pronounced in the frontotemporal regions. These effects, considered consistent with those produced by a "desipramine-like" antidepressant, reached a plateau from 10 to 24 hours for the ER formulation.

The time to peak nausea was not significantly different between the CF and ER formulations: 2.36 and 3.10 hours post-dose, respectively. The dose-adjusted AUC for nausea with the ER formulation was about 63% less than that for the CF formulation.

8.1.10 Withdrawal Phenomena/Abuse Potential

Abuse potential of venlafaxine ER have not been systematically evaluated. Based on in vitro receptor data and animal studies which assessed for CNS stimulant or depressant effects (submitted in NDA 20,151 for Effexor), venlafaxine HCl was not designated as a controlled substance.

Discontinuation effects have likewise not been systematically studied. Within the three placebo-controlled studies, the sponsor retrospectively identified the following events as emerging during taper or after the last dose of medication and at an incidence ≥3% in the venlafaxine ER group, which was at least twice the placebo incidence: dizziness, dry mouth, insomnia, nausea, nervousness, and seating. In the venlafaxine ER clinical trials which support efficacy, tapering was achieved by reducing the daily dose by 75mg at 1 week intervals.

8.1.11 Human Reproduction Data

Two pregnancies were reported during the clinical trials in this development program:

- Patient 36535-002 was 28 y.o. and took a mean venlafaxine ER dose of 74 mg/day, with an estimated fetal exposure of 46 days. She had an elective abortion.

- Patient 36905-006 was 39 y.o. and took a mean venlafaxine ER dose of 268.9 mg/day, with an estimated fetal exposure of 30 days. She had an elective abortion, followed by tubal ligation.

These cases provide no information regarding the effect of venlafaxine ER on human pregnancy. There are no adequate and well-controlled studies of venlafaxine use in human pregnancy.

Venlafaxine is designated Pregnancy Category C on the basis of data from rats: there was a decrease in pup weight, an increase in stillbirth, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning; the no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis.

8.1.12 Overdose Experience

Two venlafaxine ER patients attempted suicide by taking an overdose of venlafaxine ER, either alone or with other drugs:

- Patient 36515-001, a 52 y.o. female, ingested 6 grams of venlafaxine ER and 2.5 mg of lorazepam. She was hospitalized, treated with gastric lavage, and recovered without sequelae.

- Patient 36532-001, a 27 y.o. female, took 2.85 grams of venlafaxine ER (thirty-eight 75mg capsules). On admission, she reported paresthesia in all four extremities. She recovered without sequelae.

In response to a report of a fatal overdose that appeared to involve venlafaxine alone (Mfr. Report #8-96271-004B), the sponsor had amended Effexor labeling to indicate that overdose fatalities have involved predominently combined use with alcohol and/or other drugs. This labeling change, which was reported to the Agency in the 12th Quarterly Adverse Event Report to NDA 20,151, should be incorporated into the corresponding section of Effexor XR labeling.

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8.2 Review of Systems

8.2.1 Cardiovascular

8.2.1.1 Adequacy of Assessment

Within the Phase 3 database (N-venER=705), cardiovascular adverse events were regularly documented and vital signs (pulse and blood pressure) were assessed as indicated in Table 8.1.7.1. ECG's were recorded as in Table Appendix 8.1.8.1 in about 550 venlafaxine ER patients. These evaluations are felt to be adequate to evaluate the effect of venlafaxine ER on the cardiovascular system.

8.2.1.2 Cardiovascular Events Likely to be Drug-Related

8.2.1.2.1 Hypertension

Hypertension was reported as an adverse event in 5.2% (10/192) of the venlafaxine ER patients and 0.5% (1/202) of placebo patients in the pool of domestic, placebo-controlled studies (208 and 209); this difference is highly statistically significant (p=0.005).

The mean change in supine diastolic blood pressure was +1.206 mmHg in venlafaxine ER versus -0.176 mmHg in placebo patients, a statistically significant difference between groups (p=0.009). Similarly, venlafaxine ER patients experienced a significantly higher change in supine systolic blood pressure compared to placebo: +0.468 vs. -0.884 mmHg; p=0.034).

Examination of the proportions of patients who met criteria for a potentially significant increase in blood pressure (as defined in Appendix 8.1.7.3.2.1) reveals slightly higher rates in the drug group versus placebo:

	Ven ER	Placebo	p-value
↑ supine DBP	2.0%	0.4%	0.083
↑ supine SBP	0.8%	0.0%	0.258

Fourteen of the Phase 3 venlafaxine ER patients[1] (or 2.0% of the 705 venlafaxine ER patients) were identified by the sponsor's medical monitor as having clinically significant elevation in blood pressure. The individual patient profiles for these 14 patients were examined. Patient 36726-185, a 52 year old male, experienced both the largest increase from baseline in supine

[1]Patients 20903-006, 20905-021, 20908-017, 20910-002, 36525-002, 36538-002, 36702-012, 36726-185, 36727-006, 36741-002, 36901-005, 36907-006, 36907-009, and 36909-002.

diastolic blood pressure (83→120 mmHg) as well as the highest supine diastolic blood pressure (120 mmHg)(both at week 4). The increase from baseline in supine systolic blood pressure was also sizable (131→170 mmHg). This patient experienced dizziness which may have been causally related to increased blood pressure. Also, a large postural change in blood pressure was noted in this patient (167/115 supine → 135/95 standing). This patient completed the study.

Eight venlafaxine ER patients with hypertension had events classified as serious: all 8 patients[2] are among the 14 designated above as having clinically significant BP elevations. Patient narratives for these 8 patients were reviewed: all blood pressure elevations were felt to be possibly related to drug although none of these patients experienced a consequential clinical event that could be linked to a blood pressure elevation (e.g. stroke or myocardial infarction).

In the total Phase 3 database, 0.7% (5/705) of the venlafaxine ER and 0.4% (1/285) of the placebo patients dropped out due to elevations in blood pressure. Three patients[3] had histories of hypertension or borderline hypertension. One patient[4] was receiving an oral contraceptive, which has been associated with hypertension.

The sizes of the supine blood pressure (SBP) increases for these five patients are displayed in Table 8.2.1.2.1.1, with the maximum blood pressure being that with the highest supine diastolic value while on drug.

Table 8.2.1.2.1.1:
Blood Pressure Changes Among Venlafaxine ER Dropouts due to Elevated Blood Pressure

Patient #	Baseline SBP (mmHg)	Maximum SBP (mmHg)
20908-017	135/86	136/102
20910-002	142/94	170/110
36727-006	118/82	152/94
36907-009	132/89	140/98

[2]20903-006, 20905-021, 20908-017, 20910-002, 36901-005, 36907-006, 36907-009, and 36909-002.

[3]20903-006, 20910-002, and 36907-006.

[4]36525-002.

36909-002	111/85	140/108

Effect of Baseline Blood Pressure on Blood Pressure Changes

The sponsor conducted analyses to evaluate the effects of baseline SDBP (supine diastolic blood pressure) on SDBP changes during treatment. It is noted that patients with treated, controlled hypertension and those with mild inadequately-treated hypertension were not excluded from Phase 3 studies.

The sponsor enumerated patients by the mean change in supine diastolic blood pressure for 701 venlafaxine ER and 280 placebo Phase 3 patients who were categorized by baseline value. Results are displayed in Table 8.2.1.2.1.2.

Table 8.2.1.2.1.2: Enumeration of Patients by Baseline SDBP and by Mean Change in SDBP (mmHg)

Baseline SDBP ↓	Venlafaxine ER				Placebo			
	Mean Δ in SDBP				Mean Δ in SDBP			
	<10	10-15	16-20	>20	<10	10-15	16-20	>20
<80	383	18	4	1	169	6	1	0
80-90	254	8	6	0	93	0	0	0
91-104	27	0	0	0	11	0	0	0
Total	664	26	10	1	273	6	1	0

Among venlafaxine patients, 5.3% (37/701) had a mean increase in SDBP of ≥10 mmHg. Those with baseline SDBP <91 mmHg more frequently had increases in SDBP ≥ 10 mmHg compared to those with higher baseline SDBP (5.5% vs. 0.0%); a similar pattern was seen in the placebo group (2.6% vs. 0.0%). However, this must be cautiously interpreted due to the relatively small number of patients with higher baseline readings. Only one venlafaxine ER patient experienced a mean increase >20 mmHg; that patient had a baseline reading <80. No placebo patient had a mean increase >20 mmHg.

In another categorical analysis depicting the relationship between baseline blood pressure and final blood pressure, the sponsor again grouped all venlafaxine ER and placebo patients in Phase 3 studies by categories of baseline supine diastolic blood pressure (SDBP) and then enumerated patients by 1) the final SDBP

reading and 2) the mean SDBP reading. The results are shown in Table 8.2.1.2.1.3. (Some venlafaxine ER patients were enumerated twice, once for short-term and once for long-term study participation.)

Table 8.2.1.2.1.3:
Enumeration of Patients by Baseline SDBP and Final/Mean SDBP (mmHg)

	Venlafaxine ER (N=714)			Placebo (N=287)		
	Baseline SDBP			Baseline SDBP		
	≤90	91-104	>104	≤90	91-104	>104
Final SDBP						
≤90	650	23	0	270	8	0
91-104	34	3	0	6	3	0
>104	3	1	0	0	0	0
Mean SDBP						
≤90	660	15	0	274	5	0
91-104	26	12	0	2	6	0
>104	1	0	0	0	0	0

In the evaluation of <u>final</u> SDBP readings, 5.3% (38/714) venlafaxine ER patients shifted to a higher blood pressure category; 0.4% (3/714) moved from the normal range (≤90) to the moderately elevated range (>104). In the placebo group, 2.1% (6/287) shifted to a higher range, with no shifts from normal to moderate elevation (>104).

In the analysis of <u>mean</u> SDBP readings, 3.8% (27/714) of venlafaxine ER versus 0.7% (2/287) of placebo patients shifted to higher categories.

The sponsor indicates that these results are similar to those in the premarketing database for immediate-release venlafaxine.

<u>Incidence of Sustained Blood Pressure</u>

The incidence of sustained increases in SDBP was examined by the sponsor for venlafaxine ER patients across all Phase 3 studies. A sustained elevation in SDBP was defined as a treatment-emergent

increase from baseline in SDBP ≥10mmHg to a value ≥90mmHg for at least 3 consecutive visits.

Nineteen venlafaxine ER patients (2.7% or 19/705), treated with mean daily doses of 75-300 mg/day, met these criteria. When patients were stratified by mean daily dose ranges, there was no evidence of dose-response in terms of the incidence of sustained SDBP (see Table 8.2.1.2.1.4 below). Corresponding data for the placebo group was not available. The mean increase in SDBP measurements that met criteria for sustained elevations in these patients was 15.2 (±5.2) mmHg.

Table 8.2.1.2.1.4:
Proportions of Venlafaxine ER Patients with Sustained SDBP by Mean Daily Dose

Mean Daily Dose	%
≤100 mg/day	3.4% (9/264)
101 - 200 mg/day	2.1% (8/373)
201-300 mg/day	3.6% (2/55)
>300 mg/day	0.0% (0/8)

Dose-Response for Blood Pressure

The adjusted mean supine diastolic blood pressure (SDBP) values by venlafaxine ER dose group (75 and 150 mg/day) were examined in the short-term, fixed dose study (367). Table 8.2.1.2.1.5 summarizes this data: there is no evidence of dose-response for SDBP in this analysis, although this must be cautiously interpreted since only these two dose groups were examined.

Table 8.2.1.2.1.5:
Adjusted Mean SDBP by Dose Group (Study 367)

	VEN ER 75 MG/DAY		VEN ER 150 MG/DAY	
	N	Mean SDBP ±SE	N	Mean SDBP ±SE
Week 1	81	76.4 ±0.7	79	76.4 ±0.8
Week 2	78	78.0 ±0.7	69	76.4 ±0.8
Week 4	70	77.9 ±0.9	62	77.6 ±1.0
Week 6	59	78.7 ±1.1	56	77.5 ±1.1
Week 8	56	76.2 ±1.0	51	76.3 ±1.0

Fixed dose data from the venlafaxine (IR) pre-marketing studies revealed virtually no mean change in supine DBP at doses of 75 and 225 mg/day, with an increase of 7.2 mmHg at 375 mg/day;[5] therefore, the dose range in this study may be inadequate to fully explore a dose-effect relationship.

8.2.1.2.2 QT Interval Prolongation

Within the pool of placebo-controlled studies, the mean change from baseline in QTc was significantly higher in the venlafaxine ER group compared to placebo (+4.7 vs. -1.9 msec; p=0.033).[6] A comparison of venlafaxine ER to venlafaxine IR in study 208 a similar result (+9.8 vs. -3.8 msec, respectively; p=0.056).

Changes in the uncorrected QT interval were not significantly different between drug and placebo: this difference from the corrected QT finding is likely explained by the higher mean change in heartrate in the venlafaxine ER patients relative to placebo (+4.0 vs. +0.9 bpm; p<0.001).

Data from the fixed dose study (367) did not suggest that QTc prolongation was dose related: mean change from baseline in the 75mg group was +2.2 msec vs. -1.5 msec in the 150mg group; however, caution is advised since this study did not explore a wide range of doses.

Consideration of the proportions of patients who met criteria for a potentially clinically significant change in QTc (increase ≥10% from baseline and > 440 msec) revealed a higher fraction of venlafaxine ER patients who met these criteria compared to placebo in the placebo-controlled study pool (4% vs. 1%; p=0.041). Comparing venlafaxine ER to venlafaxine IR in study 208, a similar finding was discovered (7% vs. 1%; p=0.119). Across all Phase 3 studies, 5% (30/553) of the venlafaxine ER patients met these criteria. Of these 30 patients, 3 had QTc values over 500 msec: these cases will be described below. No placebo or venlafaxine IR patients had a QTc >500 msec.

- Patient 36505-101 was a 68 y.o. female who dropped out after 15 days of treatment with venlafaxine ER 75 mg/day because of nausea. She also had an increased heartrate at the time of dropout (120 bpm from 96 bpm at baseline). The baseline QTc was 437 msec; two weeks after the last dose, her QTc was 572 msec.

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[5]Effexor labeling.

[6] See 2/13/97 submission of corrected statistics regarding mean change from baseline for QTc.

• Patient 36512-002 was a 57 y.o. female with a baseline QTc of 350 msec, which was increased to 574 msec at the six month visit. There were no cardiac symptoms reported during treatment and no other ECG's were performed.

• Patient 36906-002 was a 51 y.o. female who dropped out after 8 weeks of venlafaxine ER 150 mg/day due to ECG changes. Her baseline ECG revealed non-specific ST-T changes and a QTc of 448 msec. An ECG on Day 29 revealed possible right atrial enlargement, possible anterolateral ischemia, and increase ST-T abnormality with a QTc of 380 msec. QTc at dropout was 503 msec with continued ST-T changes. The patient experienced persistent dizziness from Day 21.

A fourth patient (36728-002) was reported to have an on-drug QTc of 739 msec (baseline= 408 msec) in the original ISS submission. However, the sponsor, in a 1/27/97 submission, indicated that the on-therapy value was erroneous and that the correct QTc was 412 msec.

In terms of adverse events that might represent outcomes of QT interval prolongation in Phase 3 venlafaxine ER treated patients, there was only one unexplained death in this database (patient 36524-009); as will be discussed in section 3.2.1.3.1 below, on-drug ECG data is not available and this fatality is not felt to be reasonably linked to venlafaxine ER treatment. Other such cardiac events among Phase 3 venlafaxine ER patients are as follows: syncope (3 cases: 36704-003, 36902-002, and 36906-011),[7] myocardial infarction (36905-004), angina (2 cases: 36532-002 and 36908-003), and bigeminy (36902-006).[8] A review of the ECG data from these cases provides no evidence that these events were associated with QT prolongation. However, ECG data is relatively sparse and this lack of data can in no way rule out such an association.

8.2.1.2.3 Vasodilatation

Adverse events coded as vasodilatation, mostly "hot flashes," were reported in 6% of the venlafaxine ER and 1% of the placebo patients in the pool of studies 208 and 209 (p=0.029).

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[7]The rates of syncope in the total Phase 3 database (per 100 PEY's) were 1.9 for venlafaxine ER and 4.7 for placebo.

[8]36902-006 was taking multiple concomitant medications for asthma. She developed a bigeminal rhythm (with palpitations) and was withdrawn from the study. QTc was 394 msec and essentially unchanged from baseline. Normal rhythm was present after discontinuation of venlafaxine ER.

In the Phase 3 integrated database, only one venlafaxine ER patient (36717-007) dropped out due to vasodilatation (feeling "excessive heat" and sweating); one placebo patient dropped out due to this event (dropout rate of 0.1% for venlafaxine ER and 0.4% for placebo); thus, among the Phase 3 venlafaxine ER patients who reported vasodilatation, only 1 in 25 dropped out for this reason.

8.2.1.3 Cardiovascular Events Unlikely to be Drug-Related

8.2.1.3.1 Deaths

The death of patient 36524-009, a 72 y.o. female with controlled hypertension and diabetes with a listed cause of death as "acute pulmonary edema," may have been linked to an acute cardiac event. Baseline QTc was 450 msec; no on-drug ECG was recorded. Given her age, history of diabetes, previous uneventful treatment with venlafaxine IR, and duration of exposure to venlafaxine ER (7 months), this death is not felt to be reasonably attributable to the study drug.

8.2.1.3.2 Other Serious Adverse Events

Patient 36905-004 was a 45 y.o. obese male with insulin-dependent diabetes who was treated with venlafaxine 225 mg/day for 77 days when he presented to an emergency room with chest pain and cough. He was discontinued from the study and, the next day, cardiac work-up suggested a subendocardial infarction. Cardiac catheterization revealed 2 "blocked" coronary arteries; he underwent angioplasty about one week after dropout. This event is judged to be unlikely related to venlafaxine ER treatment.

8.2.1.3.3 Dropouts due to Adverse Events

Cardiovascular events not previously mentioned which led to dropout among venlafaxine ER patients in the Phase 3 database (and the number of dropouts for that event) are migraine (1), palpitations (2), and tachycardia (1).

Patient 36511-002 dropped out for tachycardia after experiencing increase in heartrate from 84 to 90 bpm; this finding resolved after drug discontinuation.

When the total incidence (per 100 PEY's) of each event in the Phase 3 database is compared between drug and placebo, a relationship to drug seems doubtful:

	Venlafaxine ER	Placebo
Migraine	6.2	16.5
Palpitations	9.3	14.2
Tachycardia	2.5	2.4

8.2.1.3.4 Other Findings Not Felt to be Drug Related

The mean change from baseline in heartrate as recorded by ECG in the placebo-controlled study pool was larger for drug than for placebo to a highly statistically significant degree: +4.0 bpm for venlafaxine ER versus +0.9 bpm for placebo ($p<0.001$). However, the corresponding changes from baseline in supine pulse were not significantly different: +1.5 bpm for drug and +1.0 bpm for placebo. Within the pool of studies 208 and 209, the incidence of tachycardia reported as an adverse event was 0.5% for both treatment groups. In sum, the totality of evidence does not support a relationship between clinically significant tachycardia and venlafaxine ER treatment.

It is noted that 32% (112/354) of the venlafaxine ER and 25% (69/282) of the placebo patients in the pool of placebo-controlled studies met the criterion for potentially clinically significant postural decreases in diastolic blood pressure (postural decrease of ≥10 mmHg); this difference in proportions is statistically significant ($p=0.052$). The large proportions in each group suggest that the criterion is set too low to clearly reflect the numbers of patients with truly important changes. No venlafaxine ER or placebo patient in any Phase 3 study dropped out due to orthostatic hypotension; by the sponsor's analysis of these patients, it is indicated that most of the postural changes were mild to moderate and were not accompanied by symptoms in any patient. Also, the hint of drug associated postural diastolic hypotension is not consistent with the proportion meeting the criterion for a potentially significant postural drop in systolic blood pressure, which was actually higher in the placebo group. Furthermore, it is not consistent with the more clear association of blood pressure elevation with drug treatment. Thus, considering the entire body of data, it cannot be reasonably concluded that venlafaxine ER is associated with significant postural changes in diastolic BP.

The mean change from baseline in the PR interval was significantly different between venlafaxine ER and placebo: -1.693 vs. +3.541 msec, respectively; $p=0.002$. This small mean decrease for drug is likely clinically insignificant.

8.2.1.4 Summary and Conclusions

A consistent finding across a number of approaches to examining

the vital sign data was that venlafaxine ER is associated with increases in blood pressure, particularly supine diastolic blood pressure, likely the most clinically relevant variable. While none of these study patients appeared to experience important adverse events directly attributable to drug-induced hypertension, the durations of exposure in this database are likely inadequate to detect the long-term consequences of moderate blood pressure elevation.

These data also suggest that venlafaxine ER may be associated with prolongation of the QT interval in some patients. However, there did not appear to be an excessive number of clinical events that have been associated with QT prolongation among venlafaxine ER patients (e.g. sudden unexplained death, syncope, ventricular arrhythmias). Also, this must be tempered by the fact that no such ECG finding was evident in the NDA review of the immediate-release formulation and that monitoring of post-marketing reports have not provided evidence of any important cardiac concerns with the IR formulation.

Venlafaxine ER was associated with vasodilatation, mostly "hot flashes," which led to the dropout of only one venlafaxine ER patient. This is appears to be a benign adverse event for most patients.

8.2.2 Digestive System

8.2.2.1 Adequacy of Assessment

Phase 3 studies monitored gastrointestinal adverse events as well as laboratory variables that reflect disturbances in hepatic function (see Appendix 8.1.6.1). This is felt to be adequate to assess the effect of venlafaxine ER on the digestive system.

8.2.2.2 Events Likely to be Drug-Related

8.2.2.2.1 Nausea

In the pool of studies 208 and 209, nausea was reported in 41% of venlafaxine ER and 14% of placebo patients ($p<0.001$). For the Phase 3 database, nausea led to premature discontinuation in 4% (26/705) of venlafaxine ER and <1% (1/285) of placebo patients; thus, 1 venlafaxine ER patient in 8 with nausea dropped out for this event.

Data from study 367 suggests that this event may be dose-related (incidence of 16% in the 75 mg/day group and 23% in the 150 mg/day group). There is evidence that patients develop tolerance to nausea (see Table 8.1.5.4.2).

Vomiting, a symptom frequently accompanying nausea, was observed in 4% of venlafaxine ER patients within the pool of 208 and 209

(versus 2% for placebo). Vomiting led to dropout in 1.3% (9/705) Phase 3 venlafaxine ER patients.

8.2.2.2.2 Dry Mouth

In studies 208 and 209, dry mouth was reported as an adverse event in 17% of venlafaxine ER and 8% of placebo patients (p=0.010). In the entire Phase 3 database, dry mouth resulted in premature discontinuation in <1% (4/705) of venlafaxine ER and 0% (0/285) of placebo patients. Thus amounts to one drug patient in 24 with dry mouth dropping out for this adverse event.

Analysis of data from study 367 did not suggest dose relationship.

8.2.2.2.3 Constipation

In the pool of 208 and 209, constipation occurred in 14% of venlafaxine ER and 6% of placebo patients (p=0.016). For the entire Phase 3 database, constipation resulted in premature discontinuation in <1% (5/705) of venlafaxine ER and 0% (0/285) of placebo patients; one venlafaxine ER patient in 14 with constipation prematurely discontinued for this reason.

Data from the fixed dose study (367) did hint that this event may be dose-related (1% incidence in the 75mg dose group and 4% in the 150mg dose group). There is evidence that many patients adapt to constipation (see Table 8.1.5.4.2), probably explaining the low dropout rate for this event.

No serious sequelae of constipation (e.g. intestinal obstruction) were noted among venlafaxine ER patients. Rectal disorders were experienced by 2% of venlafaxine ER and 0% of placebo patients in studies 208 and 209; these events represented mostly hemorrhoids, which may be related to constipation.

8.2.2.2.4 Anorexia

In the pool of studies 208 and 209, anorexia was reported in 13% of venlafaxine ER and 4% of placebo patients (p=0.002). For the entire Phase 3 database, anorexia led to dropout in <1% (7/705) of venlafaxine ER and <1% (1/285) of placebo patients. Among Phase 3 venlafaxine ER patients with anorexia, 1 in 6 dropped out for this event.

Data from the fixed dose study (367) did not suggest that this event is dose-related. There is evidence of the development of tolerance to anorexia (see Table 8.1.5.4.2).

Anorexia may be accompanied by a decrease in body weight, which will be discussed in section 8.2.4.2.1.

There were two cases of anorexia classified as serious adverse events which were considered possibly, although not convincingly, drug related:

• Patient 20821-004 was a 22 y.o. male who had a history of ulcerative colitis and multiple GI surgeries (colectomy, ileostomy, and ileal-anal re-anastomosis). This patient experienced anorexia, diarrhea, and weight loss (6 lbs) during the study and also had mild hypokalemia (3.3 mEq/L) and albuminuria on study day 14, when he dropped out. At a poststudy visit one week later, lab tests were within normal limits and symptoms had resolved.

• Patient 36909-015 was a 36 y.o. woman who reported severe appetite suppression on day 154 of venlafaxine 375 mg/day: by study day 182, her weight had dropped from 197 lbs at baseline to 179.5 lbs. She continued treatment for about another month and, at post-study follow-up several weeks after drug discontinuation, her weight loss has stopped and appetite suppression was only moderate in severity.

8.2.2.3 Events Unlikely to be Drug-Related

8.2.2.3.1 Deaths

No deaths were related to digestive system events.

8.2.2.3.2 Other Serious Adverse Events

Six venlafaxine ER patients experienced digestive system adverse events that were classified as serious but, after examination of patient summaries, were not felt to be drug related: stomach ulcer (2 patients), elevated liver enzymes (2 patients), hiatal hernia (1), and tongue lesion (1). These cases are summarized below.

• Patient 36505-301 was a 56 y.o. male with a past history of a stomach ulcer which was found to be exacerbated (on gastroscopic examination) after about 2½ months of treatment with venlafaxine ER 150 mg/day. He was treated with ranitidine and continued in the study for another 4 months, when he dropped out because of an increased headache severity.

• Patient 36903-004 was a 30 y.o. woman treated with venlafaxine ER 75 mg/day for 196 days when she experienced a stomach ulcer. She was treated with Prilosec and continued study participation.

These were the only two cases of stomach ulcer reported in the Phase 3 database. Consequently, the crude rates of stomach ulcer in this population are not significantly higher in venlafaxine ER patients compared to placebo: 0.3% (2/705) versus 0.0% (0/285);

(p=1.000).

• Patient 36901-015 was a 71 y.o. male who was found to have an SGOT level of 214 U/L on day 273 of treatment with venlafaxine ER 300 mg/day. A repeat test 4 days later showed a normal level (21 U/L). Study participation continued.

• Patient 36908-014, a 38 y.o. male who had a history of elevations in liver function tests, was found to have an SGOT level of 151 U/L on day 169 of treatment with venlafaxine ER 225 mg/day (baseline= 32 U/L). On day 203, the SGOT was 60 U/L; his dose was increased to 300 mg/day to improve response. Despite this dosage increase, subsequent SGOT values returned to normal limits.

• Patient 36902-008 was a 26 y.o. female with a history of irritable bowel syndrome and peptic ulcer disease. On day 83 of treatment with venlafaxine ER 225 mg/day, she experienced dyspepsia and symptoms of a hiatal hernia, which led to her dropout. She was treated with Tagamet after discontinuation.

• Patient 36904-004 was a 52 y.o. man who reported a tongue lesion on study day 97; he was treated with venlafaxine ER 375 mg/day. A biopsy revealed keratinizing acanthotic squamous epithelium with chronic ulceration with no evidence of malignancy. He completed the study, during which the lesion apparently disappeared. However, just before taper, the lesion reappeared and, after study completion, was reported to be resolving.

8.2.2.3.3 Dropouts due to Adverse Events

Digestive system adverse events not previously mentioned that occurred among venlafaxine ER patients and that led to study dropout (number of dropouts) are as follows: diarrhea (4), dyspepsia (4), and gastroenteritis (1). Total incidence rates of diarrhea and dyspepsia among venlafaxine ER patients in the ADR study pool were not substantially higher than in the placebo group (see Appendix 8.1.5.2.1). The crude rates of all events coded as gastroenteritis among Phase 3 patients were about the same for venlafaxine ER and placebo (0.6% and 0.7%, respectively). Thus, these events are not felt to be drug related.

8.2.2.3.4 Abnormal Liver Function Tests

Four venlafaxine ER patients in the Phase 3 database had potentially clinically significant changes in liver function tests:

• Patients 36515-009, 36520-003, and 36904-012 had elevations in total bilirubin; the last two patients had abnormal baseline

values, changes in all 3 were small in magnitude, and none had an adverse event related to hepatic dysfunction (e.g. jaundice or liver failure).

• Patient 36534-002 was a 64 y.o. male with previous multiple medical problems, to include alcohol abuse and "moderate hepatic failure;" SGOT and SGPT were elevated at baseline (2½X ULN) and were elevated further after 183 days of treatment with varying doses of venlafaxine ER (4X ULN); there were no clinical signs of hepatic dysfunction during the study (e.g. jaundice).

These cases provide no evidence of an appreciable adverse effect of venlafaxine ER on liver function.

8.2.2.4 Summary and Conclusions

In summary, it appeared that venlafaxine ER was related to the occurrence of the following digestive system adverse events: nausea, dry mouth, constipation, and anorexia. All are considered expected events for venlafaxine based on Effexor labeling.

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8.2.3 Hemic and Lymphatic System

8.2.3.1 Adequacy of Assessment

Hematologic and lymphatic adverse events were monitored regularly during all Phase 3 studies. Additionally, hematology laboratory parameters were assessed as shown in Appendix 8.1.6.1. Together, these are felt to constitute adequate assessments of the effects of venlafaxine ER on the hemic and lymphatic systems.

8.2.3.2 Events Likely to be Drug-Related

No adverse events involving the hemic or lymphatic system were deemed to be drug related.

8.2.3.3 Events Unlikely to be Drug-Related

8.2.3.3.1 Deaths

Patient 36514-002 was a 61 year old female who had received venlafaxine ER 150 mg/day for six months when she experienced thrombophlebitis. Heparin was started on an outpatient basis but she was hospitalized 12 days later, with an increase in heparin dose. She died of heart failure associated with pulmonary embolism after 7 days of hospitalization. This death was not felt to be reasonably attributable to venlafaxine ER treatment.

8.2.3.3.2 Other Serious Adverse Events

No adverse events involving the hemic or lymphatic system were classified as serious.

8.2.3.3.3 Dropouts due to Adverse Events

There was one dropout associated with a hematologic event: patient 36716-025 was involved in a motor vehicle accident and sustained contusions (coded as ecchymosis) and subsequently decided to drop out of the study. This is felt to be unrelated to drug.

8.2.3.3.4 Hematologic Laboratory Abnormalities

The mean change from baseline analysis for hematology variables revealed none for which the venlafaxine ER change was significantly greater than that for placebo. Likewise, the incidence rates for potentially clinically significant changes in hematology variables were not numerically higher in the venlafaxine ER patients compared to placebo. There were no dropouts for hematology lab abnormalities.

8.2.3.4 Summary and Conclusions

No adverse events or laboratory test abnormalities involving the hemic or lymphatic system are considered attributable to venlafaxine ER. This is consistent with the pre-marketing data for venlafaxine IR.

8.2.4 Metabolic/Nutritional System

8.2.4.1 Adequacy of Assessment

Metabolic/nutritional adverse events were monitored in all Phase 3 studies. Also, serum electrolytes, glucose, calcium, phosphorus, uric acid, cholesterol, triglycerides, total protein, and albumin were measured according the schedules listed in Appendix 8.1.6.1; body weight was measured as shown in Appendix 8.1.7.1. These assessments should be adequate to determine the metabolic and nutritional effects of venlafaxine ER.

8.2.4.2 Events Likely to be Drug-Related

8.2.4.2.1 Weight Loss

Within the pool of studies 208 and 209, weight loss was reported as an adverse event in 4% (8/192) of venlafaxine ER and 0% (0/202) of placebo patients ($p=0.003$).

The mean change in weight from baseline in the pool of studies 208, 209, and 367 was -1.151 lbs for venlafaxine ER and +1.020 lbs for placebo; this difference is also statistically significant ($p<0.001$).

A significant weight loss (≥7% of body weight) was experienced with equal frequency by venlafaxine ER patients and placebo patients in the short-term, placebo-controlled studies (2% in each group). However, if the threshold for weight loss is lowered to 5% of body weight, then 7% of venlafaxine ER patients and 2% of placebo-treated patients in placebo-controlled trials met this criterion.

Three venlafaxine ER patients with treatment-emergent weight loss had adverse events that were classified as serious: 20821-004, 36909-015, and 36534-002. The first two patients were discussed under section 8.2.2.2.4 (anorexia). The third patient was a 64 y.o. male with a history of Parkinson's disease, an intestinal fistula, gallbladder disease, and other medical conditions. After 3 months of treatment with venlafaxine ER 150 mg/day, he experienced severe agitation, dyskinesia, and a weight loss of about 26 lbs over the prior month (baseline weight 206 lbs). He was hospitalized and doses of carbidopa, levodopa, and venlafaxine ER were halved and treatment with thioridazine, lorazepam, and prazepam was instituted. He improved, was discharged, and continued participation in the study.

While these three cases hint at a drug related effect, none provide particularly convincing evidence of causality.

Few Phase 3 study patients dropped out for weight loss: venlafaxine ER 0.1% (1/705) and placebo 0.0% (0/285).

Evidence from study 367 does not suggest a dose related effect.

These data suggest that weight loss may be a drug related event associated with venlafaxine ER therapy. However, significant weight loss (≥7% body weight) was not observed more frequently among drug patients compared to placebo and few patients dropped out for this event. This effect may be linked to anorexia associated with venlafaxine ER (see section 8.2.2.2.4).

8.2.4.3 Events Unlikely to be Drug-Related

8.2.4.3.1 Deaths

No deaths were related to adverse metabolic or nutritional events.

8.2.4.3.2 Other Serious Adverse Events

Weight Gain
Two venlafaxine ER patients experienced weight gain that was classified as serious:

- Patient 36901-011 was was a 24 y.o. female treated concomitantly with Depo-Provera. She dropped out after 4½ months of treatment due to a 39 lb weight gain from baseline. Twenty-four days after dropout, she was found to have gained an additional 11 lbs.

- Patient 36907-003 was a 34 y.o. female with a history of hypothyroidism who dropped out after 5 months of treatment due to a weight gain of 13 lbs from a baseline weight of 173 lbs.

The first case is confounded by Depo-Provera administration, although the magnitude of weight gain seems excessive to be attributed only to that drug; continued weight gain after venlafaxine ER discontinuation weighs against study drug causality. The second case may be confounded by hypothyroidism.

In the pool of studies 208 and 209, weight gain was reported as an adverse event with about equal frequency in the venlafaxine ER and placebo groups (0.5% and 0.4%, respectively).

As noted above, the mean change analysis for weight actually favors weight loss, and not weight gain, as a drug related phenomenon.

The incidence of significant weight gain (i.e. an increase ≥7% of body weight) in the placebo-controlled study pool was higher in the venlafaxine ER group compared to placebo (3% vs. 1%; p=0.067).

These were the only 2 Phase 3 patients to dropout because of weight gain (dropout rates of 0.3% (2/705) for venlafaxine ER and 0.0% (0/285) for placebo).

Overall, the evidence for drug relatedness is considered weak. But significant weight gain, for whatever reason, occurred more frequently among venlafaxine ER patients.

Gout

One patient experienced gout that was considered as a serious event:

• Patient 20822-005 was a 41 y.o. male with a history of gout who experienced two exacerbations during treatment: days 11-14 and beginning day 31 for about 4 weeks. He was treated with Benemid and continued in the study. Serum uric acid level was at the high end of normal range at baseline and had actually decreased slightly at the week 12 assessment. These occurrences were not felt to be reasonably attributable to venlafaxine ER.

There was a significant mean decrease in serum uric acid among venlafaxine ER patients: -0.129 vs. +0.011 mg/dl for placebo; p=0.041). This is likely of no clinical relevance. One Phase 3 venlafaxine ER patient met the criteria for a significant increase in uric acid: 20908-018 (5 mg/dl at baseline to 8.4 on day 56); this abnormality appeared to be clinically unimportant.

8.2.4.3.3 Dropouts due to Adverse Events

One patient dropped out due to peripheral edema: patient 36516-005 was a 67 y.o. female who experienced bilateral pretibial edema associated with erythema on day 69 of treatment with venlafaxine ER 75 mg/day; she was withdrawn from the study. Etiology and follow-up information was not indicated.

Causality in this case is difficult to assess, but the crude incidence of this event in the Phase 3 database was greater in the placebo compared to the venlafaxine ER group (1.5% vs. 0.4%, respectively), suggesting a non-drug etiology.

8.2.4.3.4 Laboratory Test Abnormalities

The mean change analysis revealed a statistically significant decrease in mean serum sodium in the venlafaxine ER group compared to placebo: -0.716 vs. +0.028 mEQ/L; p=0.002. Two Phase 3 venlafaxine ER patients met the criteria for a potentially clinically significant decrease in sodium (↓ ≥5 mEQ/L

and outside normal range): 36903-009 and 36903-014. Both abnormalities were mild (level >130 mEQ/L) and neither case was associated with clinical events attributable to hyponatremia.

The mean change analysis also indicated a significantly lower mean serum chloride in drug versus placebo (-0.944 vs. +0.269 mEQ/L; p=0.002). No Phase 3 venlafaxine ER patient met the criteria for a potentially clinically significant decrease in chloride (↓ ≥5 mEQ/L and outside normal range) but one met the criteria for hyperchloremia: 20907-004. Chloride at baseline was 109, with an increase to 114 mEQ/L on day 41 of treatment; this finding did not appear to be clinically significant.

The mean change in serum cholesterol was increased in the venlafaxine ER group compared to placebo (+1.473 vs. -7.422 mg/dl; p<0.001). However, a higher percentage of placebo compared to venlafaxine ER patients had a significant increase in cholesterol (≥50 mg/dl and outside normal range) in the placebo-controlled studies (1.6% vs. 0.9%). No patient dropped out due to hypercholesterolemia. It is noted that in the pre-marketing studies for venlafaxine IR, Effexor patients had a statistically significant increase in cholesterol compared to placebo (+3 mg/dl from baseline), with unknown clinical significance. The situation with the ER formulation seems similar.

The incidence of potentially clinically significant increases in triglyceride levels was numerically higher in the venlafaxine ER groups than in the placebo group (5% vs. 3%). In studies that measured triglyceride levels (365 and 367), the patients were not required to fast before sample collection, making interpretation of this finding difficult.

Both total protein and albumin were decreased from baseline, on average; however, the decreases were significantly larger in the placebo group.

In summary, none of the laboratory findings pertinent to the metabolic/nutritional body system were felt to be clinically important.

8.2.4.4 Summary and Conclusions

Weight loss was felt to be the only clinically important, drug related adverse event in the metabolic/nutritional system. This event may be related to anorexia, which seems to be associated with venlafaxine treatment.

8.2.5 Musculoskeletal

8.2.5.1 Adequacy of Assessment

Adverse events related to the muscular and skeletal systems were

monitored regularly during studies in this development program. Also, alkaline phosphatase levels were assessed in all Phase 3 studies; elevations have been associated with some pathological bone conditions. These assessments are felt to be adequate to evaluate the effects of venlafaxine ER on this body system.

8.2.5.2 Events Likely to be Drug-Related

No musculoskeletal adverse events were felt to be drug related.

8.2.5.3 Events Unlikely to be Drug-Related

8.2.5.3.1 Deaths

There were no deaths related to events in this body system.

8.2.5.3.2 Other Serious Adverse Events

Six patients experienced adverse events classified as serious in this body system:

- Patient 36508-010 was a 61 y.o. female who sustained an L1 vertebral fracture after accidentally falling down the stairs after 2½ months of treatment.

- Patient 36511-001 underwent minor surgery due to left meniscus problem that existed prior to treatment.

- Patient 36512-005 had a pre-existing history of work related lumbar pain; he experienced an acute, severe episode of back pain after 2½ months of treatment with venlafaxine ER 150 mg/day. He was hospitalized and treated with corticosteroids and ketoprofen and continued in the study.

- Patient 36713-301 sustained a left humerus fracture in an accident on day 29 of treatment.

- Patient 36905-008 was a 52 y.o. female who underwent surgical repair of a degenerative tibial tendon tear after 203 days of venlafaxine ER treatment. She did not discontinue treatment.

- Patient 36909-005 was a 42 y.o. female who reported stress fractures in both feet on day 63 of treatment with venlafaxine ER 300 mg/day. She attributed this event to "standing all day working in a soup kitchen."

None of these events were felt to be related to venlafaxine ER therapy.

8.2.5.3.3 Dropouts due to Adverse Events

No venlafaxine ER patient dropped out for a musculoskeletal adverse event.

8.2.5.3.4 Laboratory Test Abnormalities

While it is interesting to note that the mean change in alkaline phosphatase was significantly larger in venlafaxine ER patients compared to placebo (+4.325 vs. -1.946 IU/L; p=0.001), no patient was identified as having a potentially clinically significant change in this variable. Thus, this finding is felt to have no clinical relevance.

8.2.5.4 Summary and Conclusions

There were no musculoskeletal events which were felt to be drug related.

8.2.6 Nervous System

8.2.6.1 Adequacy of Assessment

Patients in this development program were monitored for the emergence of nervous system adverse events. Changes in depressed mood were assessed using the HAM-D, MADRS, and CGI, as described in the efficacy section. Systematic data regarding abnormal movements and electroencephalographic data were not collected. The assessments performed are felt to be adequate to evaluate the effect of venlafaxine ER on the nervous system.

8.2.6.2 Events Likely to be Drug-Related

8.2.6.2.1 Dizziness

In the pool of studies 208 and 209, dizziness was reported by 30% of venlafaxine ER and 11% of placebo patients (p<0.001). In the entire Phase 3 database (studies 208, 209, 365, 367, and 369), 116 venlafaxine ER patients reported dizziness: the dropout rates for dizziness were 1.8% (13/705) for venlafaxine ER and 1.1% (3/285) for placebo. Thus, only 1 patient in 9 with this event dropped out for this reason.

Available data from study 367 did not suggest dose-relatedness.

There was evidence to indicate that a large fraction of patients with dizziness do adapt to this experience over time (see Table 8.1.5.4.2).

8.2.6.2.2 Insomnia

In studies 208 and 209, insomnia was reported by 30% of venlafaxine ER and 14% of placebo patients (p<0.001). Across the entire Phase 3 database, 104 venlafaxine ER patients reported insomnia: the dropout rates for insomnia were 0.9% (6/705) for venlafaxine ER and 0.4% (1/285) for placebo. Only 1 patient in 17 with insomnia dropped out for this event.

Available data from study 367 did not suggest dose-relatedness for insomnia.

Evidence indicated that some of patients with insomnia do adapt to this event over time (see Table 8.1.5.4.2).

8.2.6.2.3 Somnolence

In the pool of studies 208 and 209, somnolence was reported by 24% of venlafaxine ER and 10% of placebo patients (p<0.001). In the Phase 3 database, 111 venlafaxine ER patients experienced somnolence: the rates of dropout for somnolence were 1.7% (12/705) for venlafaxine ER and 0.7% (2/285) for placebo. Only 1 patient in 9 with somnolence dropped out for this reason.

Available data from study 367 did not suggest dose-relatedness.

Data indicated that many of patients with somnolence do develop tolerance to this event (see Table 8.1.5.4.2).

There were 10 venlafaxine ER patients in Phase 3 studies who experienced serious events coded as accidental injury. Since somnolence may predispose to accidents, a cursory exploration for a possible association between venlafaxine ER treatment and accidental injuries was performed. The incidence of all events classified as accidental injury in Phase 3 patients was compared between the venlafaxine ER and placebo groups. The crude incidence for venlafaxine ER was lower than that for placebo: 3.8% (27/705) vs. 4.9% (14/285). Adjusting for exposure, the difference in rates (per 100 PEY's) is even larger: 16.7 for drug and 33.0 for placebo. This mitigates against an association between venlafaxine ER treatment and accidental injuries.

8.2.6.2.4 Nervousness

In studies 208 and 209, nervousness was reported by 17% of venlafaxine ER and 6% of placebo patients (p=0.001). Among all Phase 3 patients, 60 venlafaxine ER patients reported nervousness: the dropout rates for nervousness were 0.9% (6/705) for venlafaxine ER and 1.4% (4/285) for placebo. One patient in ten with nervousness dropped out due to this event.

Data from study 367 did not suggest dose-relatedness for this event.

Evidence showed that many patients with nervousness do adapt to this event with time (see Table 8.1.5.4.2).

8.2.6.2.5 Abnormal Dreams

Among patients in studies 208 and 209, abnormal dreams (comprised mostly of vivid dreams, nightmares, and increased dreaming) was reported by 11% of venlafaxine ER and 3% of placebo patients (p=0.001). Across the Phase 3 database, 35 venlafaxine ER patients experienced events coded as abnormal dreams: the dropout rates for abnormal dreams were 0.1% (1/705) for venlafaxine ER and 0.4% (1/285) for placebo. Thus, one patient in 35 with abnormal dreams found it necessary to dropout for this reason.

Dose-relatedness was not suggested for abnormal dreams.

8.2.6.2.6 Tremor

In the pool of studies 208 and 209, tremor was reported by 6% of venlafaxine ER and 1% of placebo patients (p=0.017). For all Phase 3 patients, 33 venlafaxine ER patients reported tremor as an adverse event: the dropout rates for tremor were 0.3% (2/705) for venlafaxine ER and 0.4% (1/285) for placebo. Only about 1 patient in 17 with tremor dropped out for this event.

Data from study 367 did not suggest dose-relatedness for insomnia.

8.2.6.2.7 Decreased Libido

In patients in studies 208 and 209, decreased libido was reported by 5% of venlafaxine ER and <1% of placebo patients (p=0.032). Across the Phase 3 database, 17 venlafaxine ER patients experienced reduced libido: the dropout rates for decreased libido were 0.1% (1/705) for venlafaxine ER and 0.0% (0/285) for placebo. Thus, 1 patient in 17 with diminished sex drive dropped out for this reason.

Dose-relatedness for decreased libido was not suggested.

The effects of venlafaxine ER on sexual functioning will be discussed under section 8.2.10 (Genitourinary System).

8.2.6.2.8 Mania

The incidence of mania within the Phase 3 database was 0.3% (2/705) for venlafaxine ER and 0.0% (0/285) for placebo (p=1.000); there were no reports of hypomania. Of the 2 venlafaxine ER cases, one was considered serious:

Patient 36505-111 was a 43 y.o. male with a several year history of depression without manic episodes who presented with mania on day 34 of venlafaxine ER treatment and required hospitalization. This patient had previously completed study 367 on venlafaxine ER treatment.

While not sufficient to prove causality, this particular case does suggest a drug induced manic episode.

Antidepressant treatment has been associated with the precipitation of mania in a small percentage of patients and these data do hint that venlafaxine ER may be associated with infrequent occurrences of mania or hypomania in depressed patients.

8.2.6.3 Events Unlikely to be Drug-Related

8.2.6.3.1 Deaths

Patient 36713-102 was a 62 year old female who took venlafaxine ER 75 mg/day for 21 days before attempting suicide by hanging. She died 6 days later from her injuries.

Within the Phase 3 safety database, the incidence rates of events coded as suicide, suicide attempt, intentional overdose, or suicidal ideation, based on the number of patients with at least one of these events, were computed as follows:

Venlafaxine ER	3 per 100 PEY's
Placebo	7 per 100 PEY's

Thus, the venlafaxine ER rate was less than the placebo rate.

Additional systematic analysis, such as an evaluation of changes in item #3 of the HAM-D or item #10 of the MADRS to detect the emergence of suicidality, was not provided by the sponsor. Such analyses were done for the venlafaxine IR NDA (20,151) and, according to 6/18/93 clinical review of that submission, there was no evidence to suggest that venlafaxine IR treatment was associated with the emergence of suicidality.

8.2.6.3.2 Other Serious Adverse Events

Six venlafaxine ER patients experienced nervous system events not previously discussed that were classified as serious:

Patient 36515-007 was a 70 y.o. female who dropped out due to confusion after a month of treatment with venlafaxine ER 150 mg/day. She had been treated concomitantly with diazepam.

Patient 36526-002 was a 60 y.o. female who was hospitalized on 2 occasions for severe anxiety; treatment was stopped after the

second admission following 9 months of venlafaxine ER therapy.

Patient 36907-004 was hospitalized for an adjustment reaction after an argument with his wife.

Patient 36521-006 was a 36 y.o. male who experienced a mild left facial paralysis with hypoesthesia and a slight fever after 43 days of venlafaxine ER 75 mg/day. He was hospitalized and dropped out of the study. The presumed diagnosis was a common facial paralysis; this persisted after dropout. There were no similar events reported in this database.

Patient 36537-001 was a 61 y.o. female who was found to have an acoustic neuroma after 6 months of treatment. She discontinued treatment prior to surgery.

Patient 36727-006 was a 46 y.o. female who experienced trismus ("jaw-clenching") after 9 days of venlafaxine ER 150 mg/day which, together with insomnia, dry mouth, and blood pressure elevation, led to dropout about 2 weeks later. No other venlafaxine ER patients reported an adverse event consistent with an extrapyramidal syndrome, although such events have been infrequently reported with SSRI treatment.

None of these events were felt to be reasonably attributable to venlafaxine ER treatment.

8.2.6.3.3 Dropouts due to Adverse Events

Other nervous system adverse events that led to dropout among venlafaxine ER patients in Phase 3 studies (number of dropouts for each event) are: agitation (5), depression (3), paresthesia (2), ataxia (1), depersonalization (1), emotional lability (1), hostility (1), hypokinesia (1), reflexes decreased (1), and vertigo (1).

Some events (agitation, depression, depersonalization, and emotional lability) are not unexpected in any large sample of depressed patients. None of these were reported by more than 3% of the Phase 3 venlafaxine ER group.

A listing of all Phase 3 treatment-emergent adverse events was searched to detect the net occurrence of events that could represent hostility, aggression, or violent behavior. Only one such COSTART term was detected, namely "hostility." The incidence of hostility in the Phase 3 safety database was as follows:

Venlafaxine ER	1 per 100 PEY's
Placebo	5 per 100 PEY's

By this analysis, hostility occurred more frequently in the

placebo group and, therefore, is felt to be unlikely related to treatment with venlafaxine ER.

The rates of the remaining events (per 100 PEY's) in Phase 3 studies was examined:

	Venlafaxine ER	Placebo
Ataxia	1.9	2.4
Hypokinesia	0.6	0.0
Paresthesia	8.0	7.1
Reflexes Decreased	0.6	0.0
Vertigo	8.0	4.7

This information does not provide convincing evidence of drug relatedness for these events.

8.2.6.4 Summary and Conclusions

The following adverse events are felt to be related to venlafaxine ER treatment: dizziness, insomnia, somnolence, nervousness, abnormal dreams (vivid or increased dreaming or nightmares), tremor, and decreased libido. Also, mania may possibly be related to treatment. On the whole, the vast majority of patients with these events did not dropout due to these experiences. Adaptation to some experiences (dizziness, insomnia, somnolence, and nervousness) has been demonstrated.

8.2.7 Respiratory System

8.2.7.1 Adequacy of Assessment

Respiratory adverse events were monitored on a regular basis during the studies in this development program. This is felt to be adequate to evaluate the effects of venlafaxine ER on the respiratory system.

8.2.7.2 Events Likely to be Drug-Related

8.2.7.2.1 Yawning

In the pool of studies 208 and 209, yawning was reported by 5% of venlafaxine ER patients and 0% of the placebo patients; this incidence difference is statistically significant (p=0.001). Across all Phase 3 studies, no venlafaxine ER patient dropped out for this event although there was one dropout due to dyspnea, event that could be related to hypoxemia and yawning:

- Patient 20910-022 is a 45 y.o. woman who reported moderate shortness of breath during her first 2 days of treatment with

venlafaxine ER 75 mg/day. She continued in the study but dropped out later, on day 35, due to hypertension.

Dyspnea seems unlikely to be related to drug in this case. There was a low incidence of dyspnea in studies 208 and 209 (2% for venlafaxine ER and 1% for placebo (p=1.000). Thus, dyspnea does not appear to be drug related and, without further data (e.g. arterial blood gas results), a definitive link to hypoxemia cannot be established.

This event did not appear to be dose related in study 367.

8.2.7.3 Events Unlikely to be Drug-Related

8.2.7.3.1 Deaths

Patient 36514-002, who is described in section 8.2.3.3.1, died from a pulmonary embolism as a complication of thrombophlebitis.

8.2.7.3.2 Other Serious Adverse Events

Patient 36907-011 was a 36 y.o. woman who experienced chest pains on day 155 of treatment with venlafaxine 225 mg/day. ECG, blood gas analysis, and chest X-ray were all normal. Pleuritis was diagnosed and she was treated with ibuprofen and acetaminophen with codeine. The study drug was continued and symptomatology resolved after 16 days.

This event is not felt to be drug related.

8.2.7.3.3 Dropouts due to Adverse Events

No previously unmentioned respiratory events resulted in dropout.

8.2.7.4 Summary and Conclusions

Yawning was the only respiratory adverse event related to venlafaxine ER therapy. No patients dropped out due to this event.

8.2.8 Dermatological System

8.2.8.1 Adequacy of Assessment

Skin signs and symptoms were regularly documented during the studies in this development program. This is felt to be adequate to assess the impact of venlafaxine ER on the dermatological system.

8.2.8.2 Events Likely to be Drug-Related

8.2.8.2.1 Sweating

In the pool of the domestic, placebo-controlled studies (208 and 209), 16% of the venlafaxine ER and 3% of the placebo patients experienced sweating ($p<0.001$). Among the 90 Phase 3 venlafaxine ER patients who reported sweating, only 5 (or 1 in 18) dropped out for this reason; the incidence rates of dropout for sweating in Phase 3 were 0.7% (5/705) in the drug group and 0.0% (0/285) in the placebo group.

Data from study 367 did suggest that this adverse event was dose related (10% incidence in the 75 mg/day group and 15% in the 150 mg/day group).

Also, some adaptation to sweating is indicated (see Table 8.1.5.4.2). However, even after a month of treatment, almost two-thirds of the patients who experienced sweating in the first week still reported this adverse event.

8.2.8.3 Events Unlikely to be Drug-Related

8.2.8.3.1 Deaths

There were no deaths resulting from an adverse event in the dermatological system.

8.2.8.3.2 Other Serious Adverse Events

Ten venlafaxine ER patients experienced dermatological events that were classified as serious:

Five patients had a treatment-emergent rash, with urticaria in 3 cases (20811-005, 36522-007, 36524-002, 36903-010, and 36906-008). Two of these cases appeared to be related to environmental allergens and a third case resolved with antihistamine treatment despite continued venlafaxine ER treatment.

One patient was diagnosed with erythema nodosum after 2½ months of treatment, which persisted after drug discontinuation (36516-005). There was no concomitant medication.

Another patient experienced urticaria after 6½ months of treatment with venlafaxine 375 mg/day which resolved after treatment with Medrol and Hismanal (36909-010).

Patient 36909-011 experienced pruritus on the arms and hands on day 207 of therapy; this resolved without treatment.

Photosensitivity (severe sunburn with generalized edema) was reported by patient 36908-016 on day 178 of treatment; this was treated with lidocaine and prednisone, with resolution after 8 days; venlafaxine ER was continued.

Patient 36908-007 had a squamous papilloma removed from the left ear on day 82 of therapy; study treatment was continued.

None of these cases were felt to clearly represent a cutaneous reaction to venlafaxine ER, although a causal relationship cannot be entirely ruled out. No cases of severe skin reactions (e.g. Stevens-Johnson syndrome or toxic epidermal necrolysis) were reported in this database.

In order to further explore a possible relationship between venlafaxine ER treatment and cutaneous allergic events, the number of unique Phase 3 drug and placebo patients who experienced events coded as at least of the following terms was determined: allergic reaction, erythema nodosum, maculopapular rash, rash, pruritus, and urticaria. The crude incidence was numerically higher in the venlafaxine ER group compared to placebo (4.8% vs. 2.8%; p=0.168). Upon adjusting for differential exposure, the adjusted rates (per 100 PEY's) are similar: 21.0 and 18.9, respectively. These data do not show a particular tendency for venlafaxine ER to be associated with allergic skin events compared to placebo.

8.2.8.3.3 Dropouts due to Adverse Events

Only one dermatological event not already discussed occurred in a venlafaxine ER patient and led to dropout: patient 36908-011 was a 34 y.o. female who experienced dry skin beginning on day 57; this persisted and resulted in premature discontinuation 5 weeks later. This event was not felt to be drug related.

8.2.8.4 Summary and Conclusions

Sweating was the sole dermatological adverse event deemed to be drug related. There is evidence from the fixed dose study that sweating may be a dose related phenomenon. These safety data did not indicate a tendency for venlafaxine ER to be associated with allergic skin reactions more frequently than placebo.

8.2.9 Special Senses

8.2.9.1 Adequacy of Assessment

Studies in the venlafaxine ER development program monitored adverse events involving the special senses on a regular basis during treatment. This is felt to be sufficient to determine the influence of venlafaxine ER on special sensory functions.

8.2.9.2 Events Likely to be Drug-Related

8.2.9.2.1 Blurred Vision

Adverse events coded as abnormal vision (mostly "blurred vision" and "difficulty focusing eyes") were reported in 8% of venlafaxine ER and <1% of placebo patients in the pool of studies 208 and 209 (p=0.001). Among Phase 3 patients, dropout rates for these events were <1% (2/705) for drug and 0.0% (0/285) for placebo; 1 patient for every 12 with abnormal vision dropped out for that event.

This adverse experience did not appear to be dose related in study 367.

8.2.9.3 Events Unlikely to be Drug-Related

8.2.9.3.1 Deaths

No deaths occurred secondary to a special sense adverse event.

8.2.9.3.2 Other Serious Adverse Events

One serious adverse event occurred in this body system:

- Patient 36905-003 was a 63 y.o. female who experienced a left superior oblique ocular nerve palsy, resulting in diplopia which began after 96 days of venlafaxine ER treatment with escalating doses to 300 mg/day.

This event is not felt to be related to venlafaxine ER.

8.2.9.3.3 Dropouts due to Adverse Events

Patient 36712-002 dropped out after 12 days of treatment with venlafaxine ER 75 mg/day due to loss of taste.

The incidence of taste loss or taste perversion among Phase 3 patients was low and higher in the placebo group versus venlafaxine ER: 0.4% (3/705) of venlafaxine ER and 1.4% (4/285) of placebo patients. Thus, this event does not appear to be drug related.

8.2.9.4 Summary and Conclusions

Abnormal vision (mostly "blurred vision" and "difficulty focusing eyes") was the only special sensory event deemed likely to be drug related.

8.2.10 Genitourinary System

8.2.10.1 Adequacy of Assessment

Events relevant to the genitourinary system were documented in all studies. Additionally, serum BUN and creatinine as well as urinalysis were analyzed as depicted in Appendix 8.1.6.1. These assessments are considered adequate to study the influence of venlafaxine ER on this body system.

8.2.10.2 Events Likely to be Drug-Related

8.2.10.2.1 Abnormal Ejaculation

Within the pool of studies 208 and 209, ejaculatory difficulties were experienced by 24% of venlafaxine ER males and 0% of placebo males ($p<0.001$). These problems consisted mostly of delayed ejaculation as well as 2 cases of premature ejaculation and a patient who experienced "lack of pleasure with ejaculation." No case of retrograde ejaculation among venlafaxine ER patients was seen.

Few men with ejaculatory disturbance dropped out for this reason: across the entire Phase 3 database, dropout rates were 0.4% (2/491) in venlafaxine ER and 0.0% (0/177) in placebo male patients.

In study 367, there did appear to be a dose-response for abnormal ejaculation, with an incidence of 0% in the 75mg group and 7% in the 150mg group.

8.2.10.2.2 Impotence

In the pool of studies 208 and 209, impotence was reported by 7% of venlafaxine ER men and 1% of placebo men ($p=0.099$). In all Phase 3 studies, only one venlafaxine ER patient prematurely discontinued treatment because of impotence (dropout rate of 0.1% and 0.0% for venlafaxine ER and placebo, respectively).

Dose-relatedness was not suggested by information from study 367.

8.2.10.2.3 Abnormal Orgasm

In studies 208 and 209, abnormal orgasm was experienced by 6% of all venlafaxine ER patients and 1% of all placebo patients ($p=0.010$). When examined by gender (see Appendix 8.1.5.2.1), the

incidence for venlafaxine males and females was about equal; the relative risk[1] in females was slightly higher than that in males (7.0 vs. 4.6; relative risk ratio = 1.5).

The types of events encompassed by this event term differed slightly by gender: among males, the verbatim event terms were mostly "delayed orgasm," whereas in females, "delayed orgasm" and "anorgasmia" were reported with about equal frequency.

Among all Phase 3 patients, two male and one female venlafaxine ER patients dropped out for orgasmic difficulties (total dropout rate of 0.4% and 0.0% for venlafaxine ER and placebo, respectively).

Evidence from study 367 did not suggest a dose relationship for abnormal orgasm.

8.2.10.3 Events Unlikely to be Drug-Related

8.2.10.3.1 Deaths

No deaths were related to genitourinary adverse events.

8.2.10.3.2 Other Serious Adverse Events

Several venlafaxine ER patients experienced genitourinary adverse events that were classified as serious:

- Patient 20816-023, a 45 y.o. female, detected a breast mass on day 31 of treatment; it was subsequently removed and found to be benign.

- Patient 20818-015 was a 38 y.o. woman who dropped out on day 74 after surgery for an ovarian cyst and internal hemorrhoids.

- Patient 20901-014 was a 40 y.o. female discovered to have uterine fibroids on day 54; she continued treatment and completed the study.

- Patient 20905-021, a 36 y.o. male, experienced breast enlargement on day 34 of venlafaxine ER 225 mg/day. He had experienced a 60 lb weight gain and impotence over the prior year. He continued treatment and completed the study. Post-study he was found to have an elevated level of estradiol (59 pg/ml, with normal levels being < 50).

- 20907-004 was a 66 y.o. male who experienced urinary hesitancy on day 13 of treatment; two weeks later, he was found to have an

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[1]Venlafaxine ER:placebo.

elevated PSA (prostate specific antigen) and was subsequently diagnosed with benign prostatic hypertrophy; he completed the study.

• Patient 36716-009 was a 29 y.o. male who experienced urinary retention on day 37 of therapy; he dropped out on day 46 because of this event, which persisted.

• Patient 36906-007 was a 46 y.o. man who suffered with chronic prostatitis during the study, with onset on day 46 of treatment; he completed 225 days of therapy.

None of these events were judged to be related to venlafaxine ER therapy, with the possible exception of patient 36716-009 (urinary retention). However, a examination of the incidence of this event in the Phase 3 population did not reveal a significant difference between venlafaxine ER and placebo (0.7% vs. 0.0%, respectively; p=0.329).

8.2.10.3.3 Dropouts due to Adverse Events

Three genitourinary events not previously discussed led to dropout in 3 venlafaxine ER patients (one event in each patient): amenorrhea, urinary frequency, and urination impaired. Evaluation of the occurrence of all events in the Phase 3 database did not support a relationship to venlafaxine ER:

	Ven ER	Placebo	p-value
Amenorrhea*	1.4%	0.9%	1.000
Urinary Frequency	0.7%	1.1%	0.696
Urination Impaired	0.9%	0.0%	0.190

* Based on the number of female patients.

8.2.10.3.4 Laboratory Test Abnormalities

Although there was a significant difference between venlafaxine ER and placebo in terms of mean change from baseline for BUN (see Appendix 8.1.6.3.1.1), the mean change for drug was actually less than that for placebo. Two of the 705 Phase 3 venlafaxine ER patients had potentially clinically significant changes in BUN; however, none had such a change in serum creatinine, a more specific marker for renal dysfunction.

There were high percentages of patients with clinically significant results for urine hemoglobin/blood and urine protein/albumin (see Appendix 8.1.6.3.2.6). These findings may be an artifact of the programming algorithms used to identify positive results for these parameters. In these algorithms,

stringent limits were set so as to identify any finding other than "negative" as potentially clinically significant. The company states that careful evaluation of changes for individual patients did not reveal any reason to suspect true clinical significance in regard to these reports except for 1 patient (20821-004), who was previously discussed (section 8.2.2.2.4).

8.2.10.4 Summary and Conclusions

Abnormal ejaculation (mostly delayed ejaculation), impotence, and abnormal orgasm (mostly delayed orgasm in males and mostly delayed orgasm or anorgasmia in females) were deemed to be related to venlafaxine ER treatment in this population. Few patients dropped out due to these events. Only for abnormal ejaculation was there evidence to indicate a possible dose relationship.

8.3 Summary of Key Adverse Findings

8.3.1 Elevated Blood Pressure

Hypertension was reported as an adverse event in 5.2% (10/192) of the venlafaxine ER patients and 0.5% (1/202) of placebo patients in the pool of domestic, placebo-controlled studies (208 and 209) (p=0.005).

The mean change in supine diastolic blood pressure was +1.206 mmHg in venlafaxine ER versus -0.176 mmHg in placebo patients, a statistically significant difference between groups (p=0.009). Similarly, venlafaxine ER patients experienced a significantly higher change in supine systolic blood pressure compared to placebo: +0.468 vs. -0.884 mmHg; p=0.034).

Examination of the proportions of patients who met criteria for a potentially significant increase in blood pressure (as defined in Appendix 8.1.7.3.2.1) reveals slightly higher rates in the drug group versus placebo:

	Ven ER	Placebo	p-value
↑ supine DBP	2.0%	0.4%	0.083
↑ supine SBP	0.8%	0.0%	0.258

Eight venlafaxine ER patients with hypertension had events classified as serious: all 8 patients[2] are among the 14 designated above as having clinically significant BP elevations.

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[2]20903-006, 20905-021, 20908-017, 20910-002, 36901-005, 36907-006, 36907-009, and 36909-002.

Patient narratives for these 8 patients were reviewed: all blood pressure elevations were felt to be possibly related to drug although none of these patients experienced a consequential clinical event that could be linked to a blood pressure elevation (e.g. stroke or myocardial infarction).

In the total Phase 3 database, 0.7% (5/705) of the venlafaxine ER and 0.4% (1/285) of the placebo patients dropped out due to elevations in blood pressure.

Effect of Baseline Blood Pressure on Blood Pressure Changes

The sponsor enumerated patients by the mean change in supine diastolic blood pressure for 701 venlafaxine ER and 280 placebo Phase 3 patients who were categorized by baseline value. Results are displayed in Table 8.2.1.2.1.2.

Among venlafaxine patients, 5.3% (37/701) had a mean increase in SDBP of ≥10 mmHg. Those with baseline SDBP <91 mmHg more frequently had increases in SDBP ≥ 10 mmHg compared to those with higher baseline SDBP (5.5% vs. 0.0%); a similar pattern was seen in the placebo group (2.6% vs. 0.0%). However, this must be cautiously interpreted due to the relatively small number of patients with higher baseline readings. Only one venlafaxine ER patient experienced a mean increase >20 mmHg; that patient had a baseline reading <80. No placebo patient had a mean increase >20 mmHg.

In another categorical analysis depicting the relationship between baseline blood pressure and final blood pressure, the sponsor again grouped all venlafaxine ER and placebo patients in Phase 3 studies by categories of baseline supine diastolic blood pressure (SDBP) and then enumerated patients by 1) the final SDBP reading and 2) the mean SDBP reading. The results are shown in Table 8.2.1.2.1.3. (Some venlafaxine ER patients were enumerated twice, once for short-term and once for long-term study participation.)

In the evaluation of final SDBP readings, 5.3% (38/714) venlafaxine ER patients shifted to a higher blood pressure category; 0.4% (3/714) moved from the normal range (≤90) to the moderately elevated range (>104). In the placebo group, 2.1% (6/287) shifted to a higher range, with no shifts from normal to moderate elevation (>104).

In the analysis of mean SDBP readings, 3.8% (27/714) of venlafaxine ER versus 0.7% (2/287) of placebo patients shifted to higher categories.

The sponsor indicates that these results are similar to those in the premarketing database for immediate-release venlafaxine.

Incidence of Sustained Blood Pressure

The incidence of sustained increases in SDBP was examined by the sponsor for venlafaxine ER patients across all Phase 3 studies. A sustained elevation in SDBP was defined as a treatment-emergent increase from baseline in SDBP ≥10mmHg to a value ≥90mmHg for at least 3 consecutive visits.

Nineteen venlafaxine ER patients (2.7% or 19/705), treated with mean daily doses of 75-300 mg/day, met these criteria. When patients were stratified by mean daily dose ranges, there was no evidence of dose-response in terms of the incidence of sustained SDBP (see Table 8.2.1.2.1.4). The mean increase in SDBP measurements that met criteria for sustained elevations in these patients was 15.2 (±5.2) mmHg.

Dose-Response for Blood Pressure

The adjusted mean supine diastolic blood pressure (SDBP) values by venlafaxine ER dose group (75 and 150 mg/day) were examined in the short-term, fixed dose study (367). There is no evidence of dose-response for SDBP in this analysis, although this must be cautiously interpreted since only these two dose groups were examined.

Fixed dose data from the venlafaxine (IR) pre-marketing studies revealed virtually no mean change in supine DBP at doses of 75 and 225 mg/day, with an increase of 7.2 mmHg at 375 mg/day;[3] therefore, the dose range in this study may be inadequate to fully explore a dose-effect relationship.

8.3.2 QT Interval Prolongation

Within the pool of placebo-controlled studies, the mean change from baseline in QTc was significantly higher in the venlafaxine ER group compared to placebo (+4.7 vs. -1.9 msec; p=0.033). Curiously, a comparison of venlafaxine ER to venlafaxine IR in study 208 a similar result (+9.8 vs. -3.8 msec, respectively; p=0.056).

Changes in the uncorrected QT interval were not significantly different between drug and placebo: this difference from the corrected QT finding is likely explained by the higher mean change in heartrate in the venlafaxine ER patients relative to placebo (+4.0 vs. +0.9 bpm; p<0.001).

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[3]Effexor labeling.

Data from the fixed dose study (367) did not suggest that QTc prolongation was dose related: mean change from baseline in the 75mg group was +2.2 msec vs. -1.5 msec in the 150mg group; however, caution is advised since this study did not explore a wide range of doses.

Consideration of the proportions of patients who met criteria for a potentially clinically significant change in QTc (increase ≥10% from baseline and > 440 msec) revealed a higher fraction of venlafaxine ER patients who met these criteria compared to placebo in the placebo-controlled study pool (4% vs. 1%; p=0.041). Comparing venlafaxine ER to venlafaxine IR in study 208, a similar finding was discovered (7% vs. 1%; p=0.119). Across all Phase 3 studies, 5% (30/553) of the venlafaxine ER patients met these criteria. Of these 30 patients, 3 had QTc values over 500 msec.

In terms of adverse events that might represent outcomes of QT interval prolongation in Phase 3 venlafaxine ER treated patients, there was only one unexplained death in this database (patient 36524-009); this fatality is not felt to be reasonably linked to venlafaxine ER treatment. Other such cardiac events among Phase 3 venlafaxine ER patients are as follows: syncope (3 cases), myocardial infarction (1 case), angina (2 cases), and bigeminy (1 case). A review of the ECG data from these cases provides no evidence that these events were associated with QT prolongation. However, ECG data is relatively sparse and this lack of data can in no way rule out such an association.

These findings deserve mention in labeling but, given the degree of uncertainty regarding their actual clinical importance, prominent labeling (e.g. Warnings or Contraindication in some patients) is not felt to be warranted.

8.3.3 Vasodilatation

Adverse events coded as vasodilatation, mostly "hot flashes," were reported in 6% of the venlafaxine ER and 1% of the placebo patients in the pool of studies 208 and 209 (p=0.029).

In the Phase 3 integrated database, only one venlafaxine ER patient (36717-007) dropped out due to vasodilatation (feeling "excessive heat" and sweating).

Analysis of data from study 367 did not suggest a relationship to dose.

8.3.4 Nausea

In the pool of studies 208 and 209, nausea was reported in 41% of

venlafaxine ER and 14% of placebo patients (p<0.001). For the Phase 3 database, nausea led to premature discontinuation in 4% (26/705) of venlafaxine ER and <1% (1/285) of placebo patients.

Data from study 367 suggests that this event may be dose-related (incidence of 16% in the 75 mg/day group and 23% in the 150 mg/day group). There is evidence that patients develop tolerance to nausea (see Table 8.1.5.4.2).

8.3.5 Dry Mouth

In studies 208 and 209, dry mouth was reported as an adverse event in 17% of venlafaxine ER and 8% of placebo patients (p=0.010). In the entire Phase 3 database, dry mouth resulted in premature discontinuation in <1% (4/705) of venlafaxine ER and 0% (0/285) of placebo patients.

Analysis of data from study 367 did not suggest dose relationship.

8.3.6 Constipation

In the pool of 208 and 209, constipation occurred in 14% of venlafaxine ER and 6% of placebo patients (p=0.016). For the entire Phase 3 database, constipation resulted in premature discontinuation in <1% (5/705) of venlafaxine ER and 0% (0/285) of placebo patients.

Data from the fixed dose study (367) did hint that this event may be dose-related (1% incidence in the 75mg dose group and 4% in the 150mg dose group). There is evidence that many patients adapt to constipation (see Table 8.1.5.4.2).

No serious sequelae of constipation (e.g. intestinal obstruction) were noted among venlafaxine ER patients. Rectal disorders were experienced by 2% of venlafaxine ER and 0% of placebo patients in studies 208 and 209; these events represented mostly hemorrhoids, which may be related to constipation.

8.3.7 Anorexia

In the pool of studies 208 and 209, anorexia was reported in 13% of venlafaxine ER and 4% of placebo patients (p=0.002). For the entire Phase 3 database, anorexia led to dropout in <1% (7/705) of venlafaxine ER and <1% (1/285) of placebo patients.

Data from the fixed dose study (367) did not suggest that this event is dose-related. There is evidence of the development of tolerance to anorexia (see Table 8.1.5.4.2).

Weight loss, which may be associated with anorexia, is summarized

in the following section.

8.3.8 Weight Loss

Within the pool of studies 208 and 209, weight loss was reported as an adverse event in 4% (8/192) of venlafaxine ER and 0% (0/202) of placebo patients (p=0.003).

The mean change in weight from baseline in the pool of studies 208, 209, and 367 was -1.151 lbs for venlafaxine ER and +1.020 lbs for placebo; this difference is also statistically significant (p<0.001).

A significant weight loss (≥5% of body weight) was experienced by 7% of venlafaxine ER patients and 2% of placebo patients in the short-term, placebo-controlled studies.

Few Phase 3 study patients dropped out for weight loss: venlafaxine ER 0.1% (1/705) and placebo 0.0% (0/285).

Evidence from study 367 does not suggest a dose related effect.

This effect may be linked to anorexia associated with venlafaxine ER (see previous section).

8.3.9 Dizziness

In the pool of studies 208 and 209, dizziness was reported by 30% of venlafaxine ER and 11% of placebo patients (p<0.001). In the entire Phase 3 database (studies 208, 209, 365, 367, and 369), 116 venlafaxine ER patients reported dizziness: the dropout rates for dizziness were 1.8% (13/705) for venlafaxine ER and 1.1% (3/285) for placebo.

Available data from study 367 did not suggest dose-relatedness.

There was evidence to indicate that a large fraction of patients with dizziness do adapt to this experience over time (see Table 8.1.5.4.2).

8.3.10 Insomnia

In studies 208 and 209, insomnia was reported by 30% of venlafaxine ER and 14% of placebo patients (p<0.001). Across the entire Phase 3 database, 104 venlafaxine ER patients reported insomnia: the dropout rates for insomnia were 0.9% (6/705) for venlafaxine ER and 0.4% (1/285) for placebo.

Available data from study 367 did not suggest dose-relatedness for insomnia.

Evidence indicated that some of patients with insomnia do adapt

to this event over time (see Table 8.1.5.4.2).

8.3.11 Somnolence

In the pool of studies 208 and 209, somnolence was reported by 24% of venlafaxine ER and 10% of placebo patients ($p<0.001$). In the Phase 3 database, 111 venlafaxine ER patients experienced somnolence: the rates of dropout for somnolence were 1.7% (12/705) for venlafaxine ER and 0.7% (2/285) for placebo.

Available data from study 367 did not suggest dose-relatedness.

Data indicated that many of patients with somnolence do develop tolerance to this event (see Table 8.1.5.4.2).

8.3.12 Nervousness

In studies 208 and 209, nervousness was reported by 17% of venlafaxine ER and 6% of placebo patients ($p=0.001$). Among all Phase 3 patients, 60 venlafaxine ER patients reported nervousness: the dropout rates for nervousness were 0.9% (6/705) for venlafaxine ER and 1.4% (4/285) for placebo.

Data from study 367 did not suggest dose-relatedness for this event.

Evidence showed that many patients with nervousness do adapt to this event with time (see Table 8.1.5.4.2).

8.3.13 Abnormal Dreams

Among patients in studies 208 and 209, abnormal dreams (comprised mostly of vivid dreams, nightmares, and increased dreaming) was reported by 11% of venlafaxine ER and 3% of placebo patients ($p=0.001$). Across the Phase 3 database, 35 venlafaxine ER patients experienced events coded as abnormal dreams: the dropout rates for abnormal dreams were 0.1% (1/705) for venlafaxine ER and 0.4% (1/285) for placebo.

Dose-relatedness was not suggested for abnormal dreams.

8.3.14 Tremor

In the pool of studies 208 and 209, tremor was reported by 6% of venlafaxine ER and 1% of placebo patients ($p=0.017$). For all Phase 3 patients, 33 venlafaxine ER patients reported tremor as an adverse event: the dropout rates for tremor were 0.3% (2/705) for venlafaxine ER and 0.4% (1/285) for placebo.

Data from study 367 did not suggest dose-relatedness for insomnia.

8.3.15 Decreased Libido

In patients in studies 208 and 209, decreased libido was reported by 5% of venlafaxine ER and <1% of placebo patients (p=0.032). Across the Phase 3 database, 17 venlafaxine ER patients experienced reduced libido: the dropout rates for decreased libido were 0.1% (1/705) for venlafaxine ER and 0.0% (0/285) for placebo.

Dose-relatedness for decreased libido was not suggested.

The effects of venlafaxine ER on sexual functioning will be summarized under sections 8.3.20 to 8.3.22.

8.3.16 Mania

The incidence of mania within the Phase 3 database was 0.3% (2/705) for venlafaxine ER and 0.0% (0/285) for placebo (p=1.000). Of the 2 venlafaxine ER cases, one was considered serious. While not sufficient to prove causality, this particular case does suggest a drug induced manic episode.

Antidepressant treatment has been associated with the precipitation of mania in a small percentage of patients and these data do hint that venlafaxine ER may be associated with infrequent occurrences of mania or hypomania in depressed patients.

8.3.17 Yawning

In the pool of studies 208 and 209, yawning was reported by 5% of venlafaxine ER patients and 0% of the placebo patient (p=0.001). Across all Phase 3 studies, no venlafaxine ER patient dropped out for this event.

This event did not appear to be dose related in study 367.

8.3.18 Sweating

In the pool of the domestic, placebo-controlled studies (208 and 209), 16% of the venlafaxine ER and 3% of the placebo patients experienced sweating (p<0.001). The incidence rates of dropout for sweating in Phase 3 were 0.7% (5/705) in the drug group and 0.0% (0/285) in the placebo group.

Data from study 367 did suggest that this adverse event was dose related (10% incidence in the 75 mg/day group and 15% in the 150 mg/day group).

Also, some adaptation to sweating is indicated (see Table 8.1.5.4.2). However, even after a month of treatment, almost

two-thirds of the patients who experienced sweating in the first week still reported this adverse event.

8.3.19 Blurred Vision

Adverse events coded as abnormal vision (mostly "blurred vision" and "difficulty focusing eyes") were reported in 8% of venlafaxine ER and <1% of placebo patients in the pool of studies 208 and 209 (p=0.001). Among Phase 3 patients, dropout rates for these events were <1% (2/705) for drug and 0.0% (0/285) for placebo.

This adverse experience did not appear to be dose related in study 367.

8.3.20 Abnormal Ejaculation

Within the pool of studies 208 and 209, ejaculatory difficulties were experienced by 24% of venlafaxine ER males and 0% of placebo males (p<0.001). These problems consisted mostly of delayed ejaculation as well as 2 cases of premature ejaculation and a patient who experienced "lack of pleasure with ejaculation." No case of retrograde ejaculation among venlafaxine ER patients was seen.

Few men with ejaculatory disturbance dropped out for this reason: across the entire Phase 3 database, dropout rates were 0.4% (2/491) in venlafaxine ER and 0.0% (0/177) in placebo male patients.

In study 367, there did appear to be a dose-response for abnormal ejaculation, with an incidence of 0% in the 75mg group and 7% in the 150mg group.

8.3.21 Impotence

In the pool of studies 208 and 209, impotence was reported by 7% of venlafaxine ER men and 1% of placebo men (p=0.099). In all Phase 3 studies, only one venlafaxine ER patient prematurely discontinued treatment because of impotence (dropout rate of 0.1% and 0.0% for venlafaxine ER and placebo, respectively).

Dose-relatedness was not suggested by information from study 367.

8.3.22 Abnormal Orgasm

In studies 208 and 209, abnormal orgasm was experienced by 6% of all venlafaxine ER patients and 1% of all placebo patients (p=0.010). When examined by gender, the incidence for

venlafaxine males and females was about equal; the relative risk[5] in females was slightly higher than that in males (7.0 vs. 4.6; relative risk ratio = 1.5).

The types of events encompassed by this event term differed slightly by gender: among males, the verbatim event terms were mostly "delayed orgasm," whereas in females, "delayed orgasm" and "anorgasmia" were reported with about equal frequency.

Among all Phase 3 patients, two male and one female venlafaxine ER patients dropped out for orgasmic difficulties (total dropout rate of 0.4% and 0.0% for venlafaxine ER and placebo, respectively).

Evidence from study 367 did not suggest a dose relationship for abnormal orgasm.

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[5]Venlafaxine ER:placebo.

9.0 Labeling Review

The clinical sections of the sponsor's proposed labeling, which was submitted with the original 5/16/96 submission of this NDA, were reviewed. Relevant comments are provided below.

Clinical Trials

The first paragraph, which discusses study 208, makes reference to the efficacy of Effexor XR for the relief of symptoms of anxiety in depressed patients with associated anxiety. As discussed under the efficacy section of this review, one cannot be reasonably sure that relief of anxiety in these patients was not simply due to improvement in depression; anxious depression, or anxiety with depression, is considered to be a pseudospecific indication at this time, that is, not a diagnostic category distinct from depression itself. Such references, in the first and second sentences, should be deleted.

The second paragraph mentions the (early) time at which significant differences over placebo were observed: this information should be deleted since therapeutic onset in clinical trials cannot be characterized as simply the earliest point at which a statistically significant difference from placebo was seen. A recent article by Laska and Siegel[1] discusses an approach to evaluating time of onset which, if performed by the sponsor, might be considered in allowing pertinent information to be placed in labeling.

Also, the second paragraph presents a comparative statement regarding the efficacy of Effexor XR versus Effexor. This should be deleted since one cannot know, based on a study of this design, that therapeutically comparable doses were contrasted.

The final sentence of the second paragraph references efficacy findings in depression with anxiety; as discussed above, this should be deleted.

The third paragraph, which discusses study 209, presents data regarding time to onset which, as discussed above, should be deleted.

The last sentence of the third paragraph considers efficacy findings in depressed patients with associated anxiety; again, this should be deleted for the reasons mentioned above.

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[1]Laska EM and Siegel C. Characterizing Onset in Psychopharmacological Clinical Trials. Psychopharm Bull 1995; 31(1): 29-35.

Indications and Usage

Depression with associated anxiety and symptoms of anxiety in depressed patients with associated anxiety should be deleted as indications (see above).

It is recommended that the last paragraph be rewritten to make it more consistent with the DSM-III-R and DSM-IV descriptions of a major depressive episode. For example:

> A major depressive episode implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The lack of experience in more severely depressed, hospitalized patients should be mentioned.

Warnings

The sponsor has added two statements to the warning regarding potential interactions with MAOI's:

1) As the eighth sentence, they add: "The effects of combined use of venlafaxine and MAOI's have not been evaluated in humans or animals."

2) As an introductory phrase to the ninth sentence, they add: "Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, .."

It is not clear why these changes are added at this time but they are not considered objectionable.

The discussion of blood pressure elevation, previously included under Warnings for Effexor, is now moved to Precautions for Effexor XR. The reason for change is not clear, since the review of the venlafaxine ER database indicates that substantial blood pressure increases were documented with this formulation. It would be prudent to elevate this discussion to a Warning in Effexor XR labeling in the absence of evidence indicating a reduced risk of this event with the extended-release capsules.

Regarding the discussion of blood pressure itself, the first sentence of the first paragraph, which presents mean change data

for supine diastolic blood pressure, is felt to be inaccurate based on information presented in the sponsor's 12/19/96 submission (page 108): for venlafaxine ER, the mean increase in supine DBP was 1.2 mmHg (not <1 mmHg) and for placebo, a decrease of 0.2 mmHg (not 0.1 mmHg).

The statement regarding the risk of an increase in SDBP among patients with the highest baseline SDBP is felt to be inadequately supported by the data and should be removed. Relatively few (27) Effexor XR patients had a baseline SDBP >90 mmHg and no patient had a baseline SDBP >104 mmHg in the premarketing studies. This statement, if left in labeling, could be extrapolated to patients who have more considerably severe pretreatment hypertension than patients in this NDA safety database.

Precautions
GENERAL

In Effexor labeling, there is a section devoted to anxiety and insomnia which is conspicuously absent in the Effexor XR labeling. Granted, anxiety did not appear to be drug related based on incidence data gathered from studies 208 and 209. However, both insomnia and nervousness were felt to be drug related and, in keeping with the past format absent a reason to do otherwise, the following should be added:

Insomnia and Nervousness
Treatment-emergent insomnia and nervousness were more commonly reported for venlafaxine ER-treated patients compared to placebo-treated patients in a pooled analysis of short-term, double-blind, placebo-controlled, domestic depression studies:

Symptom	Venlafaxine ER n=192	Placebo n=202
Insomnia	30%	14%
Nervousness	17%	6%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with venlafaxine ER in Phase 3 studies.

Also, the section on changes in appetite and weight, which is present as a Precaution in Effexor labeling, has been moved to the Adverse Reactions section. Since both anorexia and weight loss were deemed to be important, drug related events in this NDA safety database, the reasoning behind this relocation is unknown. It should be moved back to this section and, since the incidence of anorexia was assessed in the pool of studies 208 and 209, this paragraph should be rewritten as follows:

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (13%) than placebo-treated patients (4%) in the pool of short-term U.S. depression studies. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of venlafaxine ER treatment. A loss of 5% or more of body weight occurred in 7% of venlafaxine ER-treated and 2% of placebo-treated patients in placebo-controlled trials. Discontinuation rates for anorexia and weight loss associated with venlafaxine ER were low (1.0% and 0.1%, respectively, of venlafaxine ER-treated patients in Phase 3 studies).

Use in Patients with Concomitant Illness

The second paragraph, which cites the lack of experience in patients with cardiac disease, fails to mention ECG findings, especially QTc prolongation. It is suggested that this paragraph be rewritten as follows:

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing. The electrocardiograms for 357 patients who received Effexor XR and 285 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials were analyzed. The mean change from baseline in corrected QT interval (Qtc) for Effexor XR-treated patients was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). Three of 705 venlafaxine ER-treated patients in Phase 3 studies experienced QTc prolongation to over 500 msec during treatment; baseline QTc was <450 msec for all three patients. No case of sudden unexplained death or serious ventricular arrhythmia, which are possible clinical sequelae of QTc prolongation, was reported in Effexor XR premarketing studies. In controlled clinical trials, the mean change from baseline in heart rate for venlafaxine ER-treated patients was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo).

USAGE IN PEDIATRIC POPULATION

This section should be renamed PEDIATRIC USE and the statement reworded as follows:

> Safety and effectiveness in pediatric patients have not been established.

Adverse Reactions

The incidence of many important adverse events appeared to be

lower in the European study (367) compared to both U.S studies (208 and 209). Primarily for this reason, study 367 was not considered poolable with studies 208 and 209 for purposes of delineating the common adverse event profile of Effexor XR. Thus, data relevant to discontinuations due to adverse experiences and the table of common adverse events should be based on the pool of the two domestic trials.

INCIDENCE IN CONTROLLED TRIALS

The sponsor's proposed ADR table (Table 1) should be replaced with that found in Appendix 8.1.5.2.1.

Accordingly, the list of common, drug related adverse events is as follows: abnormal dreams (vivid or increased dreaming and nightmares), abnormal ejaculation, abnormal orgasm, abnormal vision (blurred vision or difficulty focusing), anorexia, constipation, dizziness, dry mouth, flatulence, hypertension, impotence, insomnia, libido decreased, nausea, nervousness, somnolence, sweating, tremor, vasodilatation, and yawning.

Missing is a subsection on dose dependency of adverse events. However, the only fixed dose study eligible to provide credible data in this regard is study 367, which used only two dose levels of venlafaxine ER (75 mg/day and 150 mg/day). Since this cannot be considered a rigorous evaluation of dose relatedness, the omission of this section is not objectionable.

Interpretation of the data regarding adaptation to certain adverse experiences is difficult without a placebo comparison group, which would provide some assessment of the degree of spontaneous adverse event resolution over time. Hence, it is recommended that this discussion be deleted.

Under vital signs, the reference to blood pressure information should be changed to "Warnings" instead of "Precautions."

Under ECG changes, the heart rate data should be moved to Precautions, where QTc prolongation is discussed. This section should reference "Precautions."

The section entitled "OTHER EVENTS OBSERVED DURING THE PRE-MARKETING EVALUATION OF VENLAFAXINE" contains a table of adverse events which are not listed in the table of ADR's (Table 1) but which were reported by the patients in either Effexor (IR) or Effexor XR clinical trials (~3700 patients). This review, on the other hand, entailed the construction of a similar table only for events in the Effexor XR Phase 3 studies which are not in

Appendix 8.1.5.2.1. It is unclear what version is favored.[2] Should the proposed table be preferred for use in final labeling, it should be revised by the sponsor in accordance with the comments below:

1) correction of the number of Phase 3 Effexor XR patients (705 not 728).

2) exclusion of terms included in the ADR pool of studies 208 and 209 (Appendix 8.1.5.2.1) in lieu of the those in Table 1 (studies 208, 209, and 367).

3) replacement of several vague terms with more informative nomenclature: abdomen enlarged, allergic reaction, hangover effect, vascular disorder, gastrointestinal hemorrhage, erythrocytes abnormal, WBC abnormal, joint disorder, sleep disturbance, thinking abnormal, abnormal speech, menstrual disorder, and kidney function abnormal.

4) some terms may be reasonably combined to increase the incidence rates: bradycardia and sinus bradycardia; stomach ulcer, duodenal ulcer, and peptic ulcer syndrome; and hypoglycemia and hypoglycemic reaction.

5) the term "seizures" should be added to the Nervous System subsection as per the supplemental application to NDA 20,151 dated 11/15/95 (S-005).

Physical and Psychological Dependence

It is recommended that the discussion of discontinuation emergent adverse events, currently placed under "Dosage and Administration," be relocated to this section.

Overdosage (Human Experience)

The final paragraph in this section should be modified to indicate that overdose fatalities have involved predominently combined use with alcohol and/or other drugs, in accordance with the change to Effexor labeling which is described in the 12th Quarterly Adverse Event Report to NDA 20,151. This change was made in response to a report of a fatal overdose that appeared to involve venlafaxine alone (Mfr. Report #8-96271-004B).

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[2]Labeling for a recently approved SR preparation of a previously marketed IR product (Wellbutrin) utilized two tables, one for events in the SR database and one for other events, observed in IR clinical trials.

Dosage and Administration

Based on the sizable proportion of venlafaxine ER patients in the two positive trials (43%) who required no dose increase above 75 mg/day and who experienced efficacy which, on average, was comparable to that observed by patients at higher doses (see discussion in section 7.3.3), it is reasonable to state that the usual therapeutic dose is 75 mg/day.

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 is no known advantage to delaying titration to the usual therapeutic dose, except possibly to decrease the initial occurrence of adverse experiences, such as nausea. Thus, it is proposed that the starting dose for most patients be the usual therapeutic dose, 75 mg/day.

The choice of 300 mg/day as the maximum dose is puzzling. The efficacy of Effexor XR was demonstrated using flexible doses in the range 75-225 mg/day. By way of comparision with the immediate release formulation, data supporting the approval of Effexor (NDA 20,151) showed efficacy up to 225 mg/day and, while doses to 375 mg/day were shown to be superior to placebo in two studies (203 and 206), there was no apparent advantage (and likely an increased risk of hypertension) with higher doses. Thus, Effexor labeling limits the daily dose to 225 mg/day, with the qualification that certain patients, including more severely depressed patients, may respond to doses up to 375 mg/day, generally in three divided doses. In the case of Effexor XR, however, there is no efficacy data above 225 mg/day and safety data is somewhat limited: in Phase 3 trials, only 47 patients received mean Effexor XR doses above 225 mg/day and only 9 patients received mean doses above 300 mg/day. Thus, it is tenuous to recommend Effexor XR doses above 225 mg/day, even for a subset of more severely depressed patients. Accordingly, we are proposing that the therapeutic dose range for Effexor XR be 75-225 mg/day.

The recommended time interval for dose incrementation ("at intervals of approximately 2 weeks or more, but not less than 4 days") is confusing. An interval of 2 weeks seems appropriate based on the following considerations: 1) the controlled dose titration studies (208 and 209) employed an incrementation schedule of 75 mg/day every 2 weeks with quite positive efficacy results; 2) although steady-state concentrations of venlafaxine and O-desmethylvenlafaxine can generally be attained within a few days, the pharmacodynamic latency to therapeutic response is likely to be somewhat longer and allowing more time prior to a dose increase may yield a response that obviates the need for a

dose increase; and 3) pooled data from studies 208 and 209 suggest that 43% of the Effexor XR-treated patients had an adequate response with a daily dose no higher than 75 mg/day, the starting dose.

The reason for recommending that doses be taken with food is not clear. Two studies of the effects of food on the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine (studies 138 and 145) after the administration of Effexor XR capsules (75mg and 150mg, respectively) revealed no effect of food on pharmacokinetic parameters. This recommendation can be deleted.

10.0 Conclusions

Overall, there is sufficient evidence to support the claim of efficacy for venlafaxine ER, in doses ranging from 75-225 mg/day, in the short-term treatment of conditions consistent with DSM-III-R or DSM-IV major depressive disorder. There is adequate evidence of reasonable safety when venlafaxine ER is used in this dose range under the other conditions of use in proposed labeling.

11.0 Recommendations

It is recommended that venlafaxine ER be approved for the treatment of major depression in daily doses to 225 mg/day. It is also recommended that the sponsor be requested to address clinical labeling issues raised in section 9.0 prior to finalization of labeling.

It is noted that the 12/28/93 approval letter for Effexor stipulates Phase 4 commitments on the part of the sponsor to

Results from these studies could likely be extended to Effexor XR.

Gregory M. Dubitsky, M.D.
February 26, 1997

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

2.27.97
I agree that this NDA is approvable. See memo to file for more detailed comments.
James P. Laughren, MD

APPENDICES

APPENDIX 5.1.1.1 Table of All Studies

Phase 1: Pharmacokinetic Studies	
600B-127-US 23446	Open-label, crossover, randomized, single dose comparative bioavailability trial; normal male volunteers (n=16); venlafaxine ER dose (75 mg), venlafaxine IR dose (37.5 mg q 12 hours)
600B-134-US 24775	Open-label, crossover, randomized, 4 day comparative bioavailability trial; normal male volunteers (n=18); venlafaxine ER dose (75 mg QD), venlafaxine IR dose (37.5 mg BID)
600B-136-US 26141	Open-label, crossover, randomized, 4 day multiple dose relative bioavailability study; normal male and female volunteers (n=24); venlafaxine ER doses (75 mg BID and 150 mg QD); venlafaxine IR 3 day titration on 37.5 mg BID and 75 mg BID
600B-138-US 25771	Open-label, randomized, crossover; single dose food effect (fed/fast); normal male volunteers (n=12); venlafaxine ER dose (75 mg)
600B-143-UK 26760	Open-label, randomized, crossover, single-dose bioavailability study; normal male and female volunteers (n=24); venlafaxine ER doses (2x75 mg and 1x150 mg), venlafaxine IR dose (50 mg)
600B-144-FR 26761	Double-blind, randomized, placebo-controlled, crossover, single dose, absolute bioavailability study; normal male volunteers (n=16); venlafaxine ER dose (75 mg), venlafaxine IR dose (50 mg), venlafaxine IV dose (10 mg)
600B-145-US 26787	Open-label, randomized, crossover, single-dose, food effect (fed/fast); normal male and female volunteers (n=16); venlafaxine ER dose (150 mg)
600B-139-US 25880	Open-label, randomized, 4-day crossover; AM vs PM; normal male volunteers (n=18); venlafaxine ER dose (75 mg/day AM dose; 75 mg/day PM dose)
600B-101-JA-ER Progress report in submission	Double-blind, placebo-controlled, ascending single dose tolerance and pharmacokinetics; normal subjects (n=32 planned); venlafaxine ER doses (37.5 mg, 75 mg, 150 mg, 225 mg)
Phase 3 Studies - Controlled Studies in Depression	
600B-208-US	Multicenter, 12-week, randomized, double-blind, parallel group, flexible dose; male and female depressed patients (n=293); venlafaxine ER dose (75 mg QD which could increase after 2 weeks to 150 mg QD), venlafaxine IR dose (75 mg QD which could increase after 2 weeks to 150 mg QD)
600B-209-US 27258	Multicenter, randomized, double-blind, parallel group; flexible dose x 8 weeks, depressed male and female patients (n=197); venlafaxine ER dose (75 mg QD which could increase to 150 mg QD after 2 weeks and to 225 mg QD after 2 more weeks)

600B-367-EU	Multicenter, randomized, 8 week, double-blind, parallel group, fixed dose; male and female depressed patients (n=329); venlafaxine ER doses (75 mg QD and 150 mg QD), paroxetine (20 mg QD)
600B-211-US Progress report in submission	Multicenter, randomized, 8-week, double-blind, parallel-group, flexible dose; depressed patients (n=300 planned); venlafaxine ER dose (75 mg QD which may be increased to 150 mg QD after 2 weeks and 225 mg QD after 4 weeks); fluoxetine dose (20 mg QD which may be increased to 40 mg QD after 2 weeks and 60 mg QD after 4 weeks)
600B-360-CA Progress report in submission	Multicenter, randomized, 12-week, double-blind, parallel-group, flexible dose; depressed patients (n=336 planned); venlafaxine ER dose (75 mg QD which could increase to 150mg QD after 2 weeks and 225 mg QD after 4 weeks), fluoxetine dose (20 mg QD which could increase to 40 mg QD after 2 weeks and 60 mg QD after 4 weeks)
Phase 3: Uncontrolled Studies in Depression	
600B-365-EU	Multicenter, open-label, flexible dose, 6-12 month long-term safety evaluation; male and female depressed patients (n=251); venlafaxine ER dose (75 mg QD which can increase to 150 mg QD after 2 weeks)
600B-369-US	Multicenter, open-label, flexible dose, 6-12 month long-term safety evaluation; male and female depressed patients (n=120); venlafaxine ER dose (75 mg QD which can increase to 150 mg QD after 2 weeks, and after 4 weeks dose may be increased in 75 mg increments to a maximum of 375 mg QD at no less than 4 day intervals)
Phase 3: Studies in Generalized Anxiety Disorder	
600B-210-US Progress report in submission	Multicenter, randomized, 8-week, double-blind, dose-finding study; generalized anxiety disorder patients (n=400 planned); venlafaxine ER doses (75 mg QD fixed dose, 75 mg QD x 1 week increased to 150 mg QD for 7 weeks, and 75 mg QD for 1 week increased to 150 mg QD for 1 week, then to 225 mg QD for 6 weeks)

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APPENDIX 7.2.1.1

STUDY 208: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	Location
Barry Baumel, MD (20811)	Neuromedical Research Associates Miami Beach, FL
Lynn A. Cunningham, MD (20812)	Vine Street Clinical Research Center Springfield, IL
Bruce Diamond, PhD (20813)	Biotech Park Augusta, GA
Arthur M. Freeman, III, MD (20814)	Louisiana State University Medical Center-Shreveport Shreveport, LA
Robert W. Gibson, Jr, MD (20815)	Piedmont Research Associates Winston-Salem, NC
Barbara L. Kennedy, MD, PhD (20816)	University of Louisville Louisville, KY
Arifulla Khan, MD (20817)	University of Washington Seattle, WA
Roger O. Patrick, PhD (20818)	Belleview Family Medicine Englewood, CO
Robert A. Riesenberg, MD (20819)	BioBehavioral Research Center Decatur, GA
Ram K. Shrivastava, MD (20820)	Eastside Comprehensive Medical Services New York, NY
Stephen M. Stahl, MD, PhD (20821)	Clinical Neuroscience Research Center San Diego, CA
Kenneth J. Weiss, MD (20822)	Delaware Valley Research Associates, Inc. King of Prussia, PA

APPENDIX 7.2.1.1

STUDY 208: BASELINE DEMOGRAPHIC CHARACTERISTICS (excl. 20813)							
Treatment Groups	N	Age (years)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
VEN ER	85	40	18-70	29(34)	56(66)	76(89)	9(11)
PLAC	91	40	20-65	39(43)	52(57)	85(93)	6(7)
VEN IR	81	43	19-72	28(35)	53(65)	73(90)	8(10)

STUDY 208: COMPLETERS OVER TIME (excl. 20813)								
Treatment Groups	Randomized	ITT	Completers [N(%)]					
			Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12
VEN ER	90	85	85(100)	80(94)	73(86)	57(67)	58(68)	49(58)
PLAC	92	91	91(100)	83(91)	70(77)	59(65)	54(59)	43(47)
VEN IR	88	81	80(99)	74(91)	67(83)	55(68)	51(63)	39(48)

STUDY 208: MEAN DOSE (mg) OVER TIME (excl. 20813)						
	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12
VEN ER	74.2	76.1	134.9	135.8	138.6	138.0
VEN IR	72.5	75.8	122.7	122.1	123.4	116.5

APPENDIX 7.2.1.1

STUDY 208: MEAN CHANGE FROM BASELINE IN HAM-D TOTAL SCORE (excl. 20813)														
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	24.40	85	-4.34	85	-6.81	85	-11.44	85	-12.91	85	-13.39	85	-14.93
PLAC	91	24.56	91	-3.97	91	-5.18	91	-8.52	91	-12.91	91	-9.01	91	-8.67
VEN IR	81	23.98	81	-4.28	81	-7.28	81	-10.48	81	-11.70	81	-11.65	81	-12.46
2-sided p-values for pairwise comparisons														
ER vs. P	0.381		0.61		0.08		0.009		<0.001		<0.001		<0.001	
IR vs. P	0.220		0.67		0.03		0.08		0.01		0.02		0.002	
ER vs. IR	0.733		0.94		0.62		0.40		0.29		0.13		0.04	
OBSERVED CASES ANALYSIS														
VEN ER	85	24.40	85	-4.34	80	-6.85	73	-12.21	57	-14.21	58	-14.93	49	-16.90
PLAC	91	24.56	91	-3.97	83	-5.65	70	-9.44	59	-9.61	54	-9.91	43	-11.35
VEN IR	81	23.93	80	-4.34	74	-7.69	67	-11.69	55	-13.40	51	-13.39	39	-14.90
2-Sided p-values for pairwise comparisons														
R vs. P	0.381		0.61		0.22		0.02		<0.001		<0.001		<0.001	
IR vs. P	0.220		0.62		0.04		0.07		0.003		0.009		0.03	
ER vs. IR	0.733		0.99		0.40		0.67		0.53		0.24		0.20	

APPENDIX 7.2.1.1

STUDY 208: MEAN CHANGE FROM BASELINE IN HAM-D DEPRESSED MOOD ITEM (excl. 20813)														
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	2.75	85	-0.65	85	-0.88	85	-1.54	85	-1.71	85	-1.65	85	-1.91
PLAC	91	2.71	91	-0.42	91	-0.58	91	-0.90	91	-0.99	91	-1.01	91	-0.92
VEN IR	81	2.77	81	-0.60	81	-0.95	81	-1.37	81	-1.62	81	-1.52	81	-1.69
2-sided p-values for pairwise comparisons														
ER vs. P	0.887		0.06		0.04		<0.001		<0.001		<0.001		<0.001	
IR vs. P	0.554		0.13		0.01		0.005		<0.001		0.003		<0.001	
ER vs. IR	0.650		0.74		0.64		0.32		0.61		0.45		0.21	
OBSERVED CASES ANALYSIS														
VEN ER	85	2.75	85	-0.65	80	-0.88	73	-1.64	57	-1.96	58	-1.83	49	-2.18
PLAC	91	2.71	91	-0.42	83	-0.63	70	-1.00	59	-1.03	54	-1.07	43	-1.33
VEN IR	81	2.76	80	-0.61	74	-1.01	67	-1.48	55	-1.85	51	-1.73	39	-2.00
2-sided p-values for pairwise comparisons														
ER vs. P	0.887		0.06		0.10		<0.001		<0.001		<0.001		<0.001	
IR vs. P	0.554		0.12		0.01		0.01		<0.001		0.002		0.004	
ER vs. IR	0.650		0.79		0.37		0.37		0.58		0.61		0.42	

APPENDIX 7.2.1.1

STUDY 208: MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (excl. 20813)														
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	26.41	85	-3.72	85	-5.96	85	-12.12	85	-13.96	85	-14.35	85	-15.86
PLAC	91	26.22	91	-3.84	91	-5.01	91	-8.02	91	-8.77	91	-8.79	91	-8.32
VEN IR	81	26.36	81	-4.79	81	-7.16	81	-11.10	81	-13.12	81	-13.21	81	-13.94
2-sided p-values for pairwise comparisons														
ER vs. P	0.951		0.89		0.40		0.004		<0.001		<0.001		<0.001	
IR vs. P	0.872		0.28		0.06		0.03		0.002		0.002		<0.001	
ER vs. IR	0.820		0.24		0.30		0.48		0.56		0.43		0.20	
OBSERVED CASES ANALYSIS														
VEN ER	85	26.41	85	-3.72	80	-5.99	73	-13.10	57	-15.28	58	-16.16	49	-17.27
PLAC	91	26.22	91	-3.84	83	-5.41	70	-8.84	59	-9.75	54	-9.61	43	-11.88
VEN IR	81	26.33	80	-4.85	74	-7.58	67	-12.21	55	-15.04	51	-15.39	39	-16.72
2-Sided p-values for pairwise comparisons														
ER vs. P	0.951		0.89		0.63		0.007		<0.001		<0.001		0.01	
IR vs. P	0.872		0.26		0.08		0.04		0.002		0.001		0.03	
ER vs. IR	0.820		0.21		0.20		0.58		0.88		0.66		0.80	

APPENDIX 7.2.1.1

STUDY 208: MEAN CHANGE FROM BASELINE IN CGI-SEVERITY SCORE (excl. 20813)														
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		Week 12	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	85	4.18	85	-.32	85	-.66	85	-1.40	85	-1.56	85	-1.79	85	-2.07
PLAC	91	4.21	91	-.31	91	-.49	91	-.92	91	-1.04	91	-1.08	91	-1.00
VEN IR	81	4.09	81	-.28	81	-.64	81	-1.12	81	-1.41	81	-1.46	81	-1.51
2-sided p-values for pairwise comparisons														
ER vs. P	0.270		0.91		0.18		0.005		0.003		<0.001		<0.001	
IR vs. P	0.128		0.78		0.24		0.24		0.04		0.04		0.006	
ER vs. IR	0.683		0.70		0.89		0.11		0.38		0.07		0.003	
OBSERVED CASES ANALYSIS														
VEN ER	85	4.18	85	-0.32	80	-.66	73	-1.52	57	-1.75	58	-1.98	49	-2.20
PLAC	91	4.21	91	-.31	83	-.55	70	-1.01	59	-1.17	54	-1.19	43	-1.35
VEN IR	81	4.09	80	-.29	74	-.68	67	-1.28	55	-1.67	51	-1.75	39	-1.82
2-Sided p-values for pairwise comparisons														
ER vs. P	0.270		0.91		0.41		0.008		0.005		<0.001		<0.001	
IR vs. P	0.128		0.81		0.36		0.17		0.02		0.01		0.07	
ER vs. IR	0.683		0.73		0.92		0.22		0.69		0.27		0.13	

APPENDIX 7.2.1.2

STUDY 209: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	Location
John Carman, MD (20901)	Carman Research Atlanta, GA
Lorna Charles, MD (20902)	Southern New Jersey Medical Institute Stratford, NJ
Cal Cohn, MD (20903)	The Cohn Research Center Houston, TX
James Farrell, DO (20904)	Midwest Pharmaceutical Research, Inc. St. Peters, MO
Maurizio Fava, MD (20905)	Massachusetts General Hospital Boston, MA
John Feighner, MD (20906)	Feighner Research Institute Poway, CA
Alan Feiger, MD (20907)	Feiger PsychMed Center Wheat Ridge, CO
James Ferguson, MD (20908)	Pharmacology Research Corporation Salt Lake City, UT
Kimberly Yonkers, MD (20909)	The University of Texas Southwestern Medical Center Dallas, TX
Susanna Goldstein, MD (20910)	Center for Psychobiology New York, NY
Michael Thase, MD (20911)	University of Pittsburgh Pittsburgh, PA
Richard Weisler, MD (20912)	Holly Hill Hospital Raleigh, NC

APPENDIX 7.2.1.2

STUDY 209: BASELINE DEMOGRAPHIC CHARACTERISTICS							
Treatment Groups	N	Age (years)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
VEN ER	91	40	18-66	33(36%)	58(64%)	86(95%)	5(5%)
PLAC	100	42	21-77	41(41%)	59(59%)	97(97%)	3(3%)

STUDY 209: COMPLETERS OVER TIME								
Treatment Groups	Randomized	ITT	Completers [N(%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
VEN ER	95	91	89(98)	82(90)	82(90)	78(86)	65(71)	60(66)
PLAC	102	100	99(99)	93(93)	88(88)	80(80)	63(63)	51(51)

STUDY 209: MEAN DOSE (mg) OVER TIME						
Treatment Group	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
VEN ER	73.6	76.0	124.5	135.8	176.4	176.6

APPENDIX 7.2.1.2

STUDY 209: MEAN CHANGE FROM BASELINE IN HAM-D TOTAL SCORE														
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	24.53	91	-3.87	91	-6.51	91	-7.86	91	-9.22	91	-10.52	91	-11.66
PLAC	100	23.63	100	-3.34	100	-4.81	100	-6.34	100	-6.45	100	-7.71	100	-6.78
2-sided p-values for pairwise comparisons														
V vs. P	0.07		0.76		0.07		0.16		0.008		0.02		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	24.53	89	-3.96	82	-6.82	82	-8.11	78	-9.62	65	-11.78	60	-14.38
PLAC	100	23.63	99	-3.37	93	-4.98	88	-6.68	80	-7.23	62	-9.94	51	-9.25
2-sided p-values for pairwise comparisons														
V vs. P	0.07		0.72		0.04		0.30		0.03		0.19		<0.001	

APPENDIX 7.2.1.2

STUDY 209: MEAN CHANGE FROM BASELINE IN HAM-D DEPRESSED MOOD ITEM														
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	2.79	91	-0.60	91	-0.80	91	-1.01	91	-1.15	91	-1.31	91	-1.47
PLAC	100	2.79	100	-0.40	100	-0.56	100	-0.70	100	-0.74	100	-0.82	100	-0.71
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.09		0.08		0.02		0.005		0.002		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	2.79	89	-0.62	82	-0.79	82	-1.05	78	-1.19	65	-1.38	60	-1.82
PLAC	100	2.79	99	-0.40	93	-0.55	88	-0.77	80	-0.86	62	-1.05	51	-1.12
2-Sided p-values for pairwise comparisons														
V vs. P	N/R		0.08		0.11		0.09		0.05		0.10		0.005	

APPENDIX 7.2.1.2

STUDY 209: MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE														
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	27.99	91	-4.10	91	-6.92	91	-8.22	91	-9.69	91	-11.75	91	-12.38
PLAC	100	27.75	100	-4.38	100	-5.22	100	-6.28	100	-6.79	100	-8.54	100	-7.01
2-sided p-values for pairwise comparisons														
V vs. P	0.75		0.64		0.14		0.10		0.02		0.02		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	27.99	89	-4.19	82	-7.09	82	-8.52	78	-10.35	65	-13.42	60	-16.02
PLAC	100	27.75	98	-4.47	93	-5.39	88	-6.53	79	-7.71	63	-11.32	51	-10.14
2-Sided p-values for pairwise comparisons														
V vs. P	0.75		0.62		0.18		0.21		0.08		0.21		0.005	

APPENDIX 7.2.1.2

STUDY 209: MEAN CHANGE FROM BASELINE IN CGI-SEVERITY SCORE														
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
VEN ER	91	4.43	91	-0.29	91	-0.74	91	-0.96	91	-1.16	91	-1.42	91	-1.53
PLAC	100	4.30	100	-0.31	100	-0.44	100	-0.64	100	-0.75	100	-0.93	100	-0.82
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.56		0.03		0.03		0.004		0.004		<0.001	
OBSERVED CASES ANALYSIS														
VEN ER	91	4.43	89	-0.29	82	-0.76	81	-1.00	77	-1.25	65	-1.58	60	-1.92
PLAC	100	4.30	99	-0.31	93	-0.46	88	-0.69	80	-0.88	62	-1.23	51	-1.24
2-sided p-values for pairwise comparisons														
V vs. P	N/R		0.58		0.03		0.10		0.02		0.17		0.01	

APPENDIX 7.2.1.3

STUDY 367: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	Country
J. Hosie, MD (36701)	United Kingdom
G.D.R. Martin, MD (36703)	United Kingdom
S. Mahapatra, MD (36705)	United Kingdom
H.D. N'Guyen, MD (36708)	Belgium
J. Gros-Gean, MD (36711)	Belgium
R. Whitby, MD (36702)	United Kingdom
C.L. Langdon, MD (36704)	United Kingdom
F. Ferrero, MD (36707)	Switzerland
P. Bourgeois, MD (36709)	Belgium
A. Denayer, MD (36712)	Belgium
M. Dierick, MD (36713)	Belgium
M. Frei, MD (36716)	Switzerland
D. Bonnafoux, MD (36719)	France
C. Danic, MD (36722)	France
B. Fengler, MD (36725)	France
M. Hanus, MD (36727)	France
R. Realini, MD (36715)	Switzerland
R. Cook, MD (36717)	United Kingdom
P. Chiaroni, MD (36720)	France
M. Daurignac, MD (36723)	France
C. Géraud, MD (36726)	France
P Leclerq, MD (36728)	France
P. Legoubey, MD (36729)	France
J.P. May, MD (36731)	France
F. Mesotten, MD (36734)	Belgium
L. Ravizza, MD (36737)	Italy
Goron-Parry, MD (36741)	France

APPENDIX 7.2.1.3

STUDY 367: PRINCIPAL INVESTIGATORS	
Investigator (Site #)	Country
J.M. Letzelter, MD (36746)	France
M. Martin, MD (36730)	France
P. Thermoz, MD (36733)	France
V. Volterra, MD (36736)	Italy
A. Giavedoni, MD (36739)	Italy
D. Dassa, MD (36742)	France
J.R. Rancé (36748)	France
E. Hirsch, MD (36749)	France

APPENDIX 7.2.1.3

STUDY 367: BASELINE DEMOGRAPHIC CHARACTERISTICS							
Treatment Group	N	Age (years)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
VEN 75	83	44.9	18-77	25(30%)	58(70%)	81(98%)	2(2%)
VEN 150	78	44.3	24-74	28(36%)	50(64%)	77(99%)	1(1%)
PLAC	82	44.7	19-71	26(32%)	56(68%)	81(99%)	1(1%)
PAR	80	48.2	24-75	36(45%)	44(55%)	77(96%)	3(4%)

STUDY 367: COMPLETERS OVER TIME							
Treatment Group	Randomized	ITT	Completers [N(%)]				
			Wk 1	Wk 2	Wk 4	Wk 6	Wk 8
VEN 75	83	83	82(99)	79(95)	69(83)	58(70)	53(64)
VEN 150	82	78	75(96)	68(87)	60(77)	54(69)	48(62)
PLAC	83	82	81(99)	80(98)	66(80)	57(70)	53(65)
PAR	81	80	80(100)	73(91)	62(78)	55(69)	48(60)

APPENDIX 7.2.1.3

STUDY 367: MEAN CHANGE FROM BASELINE IN HAM-D TOTAL SCORE												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	26.5	82	-5.4	82	-9.8	82	-12.5	82	-14.5	82	-15.6
VEN 150	75	27.1	75	-3.5	75	-9.2	75	-13.4	75	-14.4	75	-14.6
PLAC	81	26.6	81	-3.7	81	-8.2	81	-11.3	81	-12.5	81	-13.1
PAR	80	26.1	80	-3.5	80	-7.2	80	-9.8	80	-10.4	80	-11.3
2-sided p-values for pairwise comparisons												
75 vs. P	0.859		0.83		0.42		0.15		0.24		0.37	
150 vs. P	0.458		0.05		0.18		0.39		0.21		0.14	
PAR vs. P	0.471		0.86		0.41		0.33		0.20		0.27	
OBSERVED CASES ANALYSIS												
VEN 75	82	26.5	82	-5.4	79	-10.2	69	-13.8	58	-17.6	53	-18.6
VEN 150	75	27.1	75	-3.5	68	-10.0	60	-15.3	54	-17.3	48	-19.5
PLAC	81	26.6	81	-3.7	80	-8.3	66	-13.4	57	-15.8	53	-16.6
PAR	80	26.1	80	-3.5	73	-8.4	62	-12.3	55	-13.8	48	-16.5
2-sided p-values for pairwise comparisons												
75 vs. P	0.859		0.83		0.15		0.19		0.35		0.06	
150 vs. P	0.458		0.05		0.10		0.76		0.26		0.18	
PAR vs. P	0.471		0.86		0.92		0.46		0.20		0.95	

APPENDIX 7.2.1.3

STUDY 367: MEAN CHANGE FROM BASELINE IN HAM-D DEPRESSED MOOD ITEM												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	2.9	82	-0.6	82	-1.2	82	-1.5	82	-1.7	82	-1.9
VEN 150	75	2.8	75	-0.4	75	-1.0	75	-1.5	75	-1.5	75	-1.6
PLAC	81	2.9	81	-0.5	81	-1.0	81	-1.3	81	-1.5	81	-1.6
PAR	80	2.8	80	-0.4	80	-0.9	80	-1.3	80	-1.4	80	-1.5
2-sided p-values for pairwise comparisons												
75 vs. P	0.509		0.31		0.94		0.43		0.93		0.81	
150 vs. P	0.417		0.27		0.09		0.43		0.29		0.16	
PAR vs. P	0.403		0.36		0.64		0.80		0.45		0.73	
OBSERVED CASES ANALYSIS												
VEN 75	82	2.9	82	-0.6	79	-1.3	69	-1.6	58	-2.1	53	-2.2
VEN 150	75	2.8	75	-0.4	68	-1.1	60	-1.6	54	-1.8	48	-2.2
PLAC	81	2.9	81	-0.5	80	-1.0	66	-1.5	57	-1.9	53	-1.9
PAR	80	2.8	80	-0.4	73	-1.0	62	-1.5	55	-1.7	48	-2.0
2-Sided p-values for pairwise comparisons												
75 vs. P	0.509		0.31		0.55		0.53		0.81		0.12	
150 vs. P	0.417		0.27		0.07		0.66		0.25		0.14	
PAR vs. P	0.403		0.36		0.87		0.93		0.31		0.67	

APPENDIX 7.2.1.3

STUDY 367: MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	29.7	82	-5.7	82	-11.1	82	-14.4	82	-16.5	82	-17.7
VEN 150	75	30.6	75	-3.3	75	-9.8	75	-15.5	75	-16.5	75	-16.8
PLAC	81	29.9	81	-4.4	81	-9.4	81	-13.0	81	-14.3	81	-14.9
PAR	79	29.3	79	-3.4	79	-7.9	79	-11.4	79	-12.3	79	-13.3
2-sided p-values for pairwise comparisons												
75 vs. P	0.816		0.28		0.77		0.15		0.26		0.36	
150 vs. P	0.442		0.18		0.20		0.42		0.25		0.17	
PAR vs. P	0.599		0.29		0.27		0.35		0.30		0.40	
OBSERVED CASES ANALYSIS												
VEN 75	82	29.7	82	-5.7	79	-11.5	69	-15.9	58	-20.1	53	-21.0
VEN 150	75	30.6	75	-3.3	68	-10.7	60	-17.6	54	-20.5	48	-22.9
PLAC	81	29.9	81	-4.4	80	-9.5	66	-15.5	57	-18.2	53	-18.9
PAR	79	29.3	79	-3.4	72	-8.9	62	-14.2	55	-16.2	48	-19.4
2-Sided p-values for pairwise comparisons												
75 vs. P	0.816		0.28		0.39		0.21		0.23		0.03	
150 vs. P	0.442		0.18		0.13		0.77		0.32		0.22	
PAR vs. P	0.599		0.29		0.70		0.46		0.30		0.78	

APPENDIX 7.2.1.3

STUDY 367: MEAN CHANGE FROM BASELINE IN CGI-SEVERITY SCORE												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
LAST OBSERVATION CARRIED FORWARD ANALYSIS												
VEN 75	82	4.7	82	-0.4	82	-1.2	82	-1.6	82	-1.9	82	-2.1
VEN 150	75	4.9	75	-0.3	75	-1.1	75	-1.8	75	-1.9	75	-2.1
PLAC	81	4.8	81	-0.3	81	-1.0	81	-1.5	81	-1.7	81	-1.9
PAR	79	4.7	79	-0.2	79	-0.7	79	-1.1	79	-1.4	79	-1.6
2-sided p-values for pairwise comparisons												
75 vs. P	0.541		0.99		0.42		0.14		0.41		0.62	
150 vs. P	0.585		0.34		0.23		0.66		0.47		0.47	
PAR vs. P	0.333		0.44		0.20		0.14		0.18		0.20	
OBSERVED CASES ANALYSIS												
VEN 75	82	4.7	82	-0.4	79	-1.3	69	-1.7	58	-2.3	53	-2.5
VEN 150	75	4.9	75	-0.3	68	-1.2	60	-2.2	54	-2.4	48	-2.8
PLAC	81	4.8	81	-0.3	80	-1.0	66	-1.7	57	-2.2	53	-2.4
PAR	79	4.7	79	-0.2	72	-0.8	62	-1.4	55	-1.8	48	-2.4
2-sided p-values for pairwise comparisons												
75 vs. P	0.541		0.99		0.23		0.09		0.40		0.25	
150 vs. P	0.585		0.34		0.18		0.99		0.63		0.79	
PAR vs. P	0.333		0.44		0.39		0.19		0.18		0.78	

APPENDIX 8.1.5.2.1

Treatment-Emergent Adverse Events Occurring in ≥1% of Venlafaxine ER Patients: Pool of Studies 208 and 209[1,2]		
	% Reporting Event	
	Ven ER (N=192)	Placebo (N=202)
Body as a Whole		
Asthenia	10%	9%
Flu Syndrome	3%	2%
Neck Pain	3%	2%
Fever	1%	<1%
Generalized Edema	1%	0%
Malaise	1%	<1%
Moniliasis	1%	<1%
Photosensitivity	1%	0%
Cardiovascular System		
Vasodilatation[3]	6%	1%
Hypertension	5%	<1%
Palpitations	3%	2%
Digestive System		
Nausea	41%	14%
Dry Mouth	17%	8%
Constipation	14%	6%
Diarrhea	14%	10%
Anorexia	13%	4%
Dyspepsia	12%	11%
Flatulence	8%	4%
Vomiting	4%	2%
Periodontal Abscess[4]	2%	<1%
Rectal Disorder[5]	2%	0%
Mouth Ulceration	1%	<1%[3]

Tooth Disorder[6]	1%	0%
Hemic/Lymphatic System		
Ecchymosis	1%	<1%
Metabolic/Nutritional		
Weight Loss	4%	0%
Nervous System		
Dizziness	30%	11%
Insomnia	30%	14%
Somnolence	24%	10%
Nervousness	17%	6%
Abnormal Dreams[7]	11%	3%
Tremor	6%	1%
Libido Decreased	5%	<1%
Confusion	4%	<1%
Paresthesia	4%	1%
Agitation	3%	2%
Depersonalization	3%	<1%
Depression	3%	<1%
Hypotonia	2%	<1%
Thinking Abnormal[8]	2%	1%
Amnesia[9]	1%	<1%
Twitching	1%	<1%
Vertigo	1%	0%
Respiratory System		
Pharyngitis	10%	8%
Sinusitis	7%	6%
Yawn	5%	0%
Bronchitis	3%	2%
Dyspnea	2%	1%
Epistaxis	1%	<1%

Skin		
Sweating	16%	3%
Rash	2%	1%
Urticaria	1%	<1%
Special Senses		
Abnormal Vision[10]	8%	<1%
Mydriasis	3%	0%
Tinnitus	2%	1%
Ear Disorder[11]	1%	0%
Ear Pain[12]	1%	<1%
Urogenital System		
Abnormal Ejaculation[13,14]	24%	0%
Impotence[14]	7%	1%
Abnormal Orgasm (Female)[15,16]	6%	<1%
Abnormal Orgasm (Male)[14,17]	6%	1%
Metrorrhagia[16]	3%	<1%
Urinary Frequency	3%	<1%
Vaginitis[16]	2%	0%
Dysuria	1%	<1%
Gynecomastia[14]	1%	0%
Prostatic Disorder[14,18]	1%	0%
Urination Impaired[19]	1%	0%

[1] Events for which the venlafaxine ER incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, accidental injury, anxiety, arthralgia, back pain, chest pain, cough increased, dysmenorrhea, emotional lability, headache, infection, migraine, myalgia, pain, and rhinitis.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "tooth abscess."
[5] Mostly hemorrhoids.
[6] Mostly bruxism.
[7] Mostly vivid dreams, nightmares, and increased dreaming.
[8] Mostly concentration difficulty.
[9] Mostly "forgetfulness."
[10] Mostly "blurred vision" and "difficulty focusing eyes."
[11] Eustachian tube dysfunction and blocked eustachian tube.
[12] Mostly "earache."
[13] Mostly "delayed ejaculation."
[14] Incidence is based on the number of male patients.
[15] Mostly "delayed orgasm" or "anorgasmia."
[16] Incidence is based on the number of female patients.
[17] Mostly "delayed orgasm."
[18] Enlarged prostate gland.
[19] Mostly urinary hesitancy.

APPENDIX 8.1.5.2.2

Categorical Incidence of Treatment-Emergent Adverse Events Reported in Venlafaxine ER Patients Within the Pool of all Phase 3 Studies (N=705) [1,2]

Body as a Whole Infrequent: abscess, allergic reaction, chills, cyst, hernia, neck rigidity, neoplasm, suicide attempt, withdrawal syndrome.

Cardiovascular Infrequent: angina pectoris, bigeminy, bundle branch block, congestive heart failure, coronary artery disease, extrasystoles, hypotension, myocardial infarction, postural hypotension, syncope, tachycardia, venous insufficiency.[3]

Digestive System Infrequent: aphthous stomatitis, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, liver function tests abnormal, rectal hemorrhage, stomach ulcer, stomatitis.

Hemic/Lymphatic System Infrequent: anemia, thrombocythemia.

Metabolic/Nutritional Frequent: weight gain. Infrequent: gout, hyperlipemia, hypokalemia, peripheral edema, thirst.

Musculoskeletal System Infrequent: arthritis, bone pain, bursitis, leg cramps, myasthenia, tenosynovitis.

Nervous System Frequent: hypertonia. Infrequent: abnormal gait, apathy, aphasia, ataxia, CNS stimulation, euphoria, facial paralysis, hostility, hyperesthesia, hyperkinesia, hypesthesia, hypokinesia, loss of consciousness,[3] manic reaction, myoclonus, neuralgia, neuropathy, nystagmus, psychotic depression, reflexes decreased, stupor, suicidal ideation, trismus.

Respiratory System Infrequent: asthma, chest congestion,[3] hiccup, hyperventilation, hypoxia, laryngitis, pleurisy,[3] pneumonia, voice alteration.

Skin Frequent: pruritis, psoriasis. Infrequent: acne, alopecia, brittle nails,[3] contact dermatitis, dry skin, eczema, erythema nodosum, exfoliative dermatitis, fungal dermatitis, herpes simplex, lichenoid dermatitis, skin discoloration, skin hypertrophy.

Special Senses Infrequent: conjunctivitis, diplopia, dry eyes, hyperacusis, otitis media, parosmia, refraction change,[3] taste loss, taste perversion, visual field defect.

Urogenital System Frequent: menstrual disorder.[4] Infrequent: albuminuria, amenorrhea,[4] bladder pain, breast neoplasm, cystitis, hematuria, menorrhagia,[4] nocturia, ovarian cyst,[4] polyuria, unintended pregnancy,[4] urinary incontinence, urinary retention, urinary tract infection, urinary urgency, uterine fibroids enlarged.[4]

[1] Excludes adverse events noted in Appendix 8.1.5.2.1.
[2] Event incidence is classified by the following criteria:
Frequent: occurring in ≥1/100 patients.
Infrequent: incidence <1/100 but ≥1/1,000 patients.
[3] COSTART term has been replaced by a more specific term.
[4] Based on the number of female patients.

Appendix 8.1.6.1: Laboratory Assessments in the Integrated Safety Database Studies		
Study	**Assessments**	**Frequency**
208	Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, phosphorus, uric acid, AST, alkaline phosphatase, bilirubin, cholesterol, total protein/albumin). Hematology (hematocrit, hemoglobin, WBC count, platelet count). Urinalysis*	Baseline, week 12.
209	Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, phosphorus, uric acid, AST, alkaline phosphatase, bilirubin, uric acid, bilirubin, cholesterol, total protein/albumin). Hematology (hematocrit, hemoglobin, WBC count, platelet count). Urinalysis*	Baseline, week 8.
367	Chemistry (BUN, creatinine, AST, ALT, alkaline phosphatase, bilirubin, cholesterol, triglycerides, total protein). Hematology (RBC count, hematocrit, hemoglobin, WBC count/diff, platelet count).	Baseline, week 8.
365	Chemistry (BUN, creatinine, AST, ALT, bilirubin, alkaline phosphatase, triglycerides) Hematology (RBC count, hematocrit, hemoglobin, WBC count, platelets).	Baseline, months 6, 12.
369	Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, phosphorus, uric acid, AST, alkaline phosphatase, bilirubin, cholesterol, total protein/albumin). Hematology (hematocrit, hemoglobin, WBC count, platelet count). Urinalysis*	Baseline, months 1, 3, 6, 9, 12.

* Specific gravity, pH, protein/albumin, glucose, ketones, and hemoglobin/blood.

Appendix 8.1.6.3.1.1: Mean Change from Baseline to Last Visit in Serum Chemistry Values in Placebo-Controlled Studies (208, 209, and 367)#					
	Venlafaxine ER		Placebo		p-value*
	Total pts.	Mean change	Total pts.	Mean change	
Sodium	160	-0.716	163	0.028	0.002
Potassium	160	-0.047	160	-0.017	0.717
Calcium	160	-0.032	163	-0.049	0.984
Chloride	160	-0.944	162	0.269	0.002
BUN	162	-0.367	164	0.021	0.078
Creatinine	291	-0.015	233	-0.011	0.271
Total bilirubin	286	-0.011	228	-0.007	0.304
ALT/SGPT	131	-1.565	69	-0.246	0.438
AST/SGOT	291	-0.308	233	-0.266	0.220
Alkaline phosphatase	289	4.325	231	-1.946	0.001
Cholesterol	290	1.473	232	-7.422	<0.001
Triglycerides	129	-2.051	68	15.532	0.211
Glucose	159	0.705	160	0.913	0.447
Uric acid	160	-0.129	163	0.011	0.041
Total protein	289	-0.074	233	-0.166	0.006
Albumin	159	-0.049	161	-0.128	0.007
Phosphorus	159	-0.043	158	-0.034	0.349

Units are those indicated in Appendix 8.1.6.3.2.1.
* p-value for the intergroup comparison of adjusted mean values at the final on-drug assessment.

Appendix 8.1.6.3.1.2: Mean Change from Baseline to Last Visit in Hematology Values in Placebo-Controlled Studies (208, 209, and 367)					
	Venlafaxine ER		Placebo		p-value *
	Total pts.	Mean change	Total pts.	Mean change	
Hematocrit (%)	290	-0.201	228	-0.785	0.029
Hemoglobin (gm%)	290	-0.043	229	-0.274	0.003
RBC count (million/cmm)	132	-0.001	69	-0.040	0.257
WBC (1000/cmm)	290	-0.221	229	-0.209	0.960
Neutrophils (%)	88	-0.645	44	-1.870	0.538
Neutrophils (1000/cmm)	41	-0.444	23	-0.163	0.201
Eosinophils (%)	85	0.074	42	0.010	0.901
Monocytes (%)	90	0.307	46	-0.311	0.211
Basophils (%)	82	-0.066	39	-0.138	0.236
Lymphocytes (%)	91	0.863	46	2.148	0.514
Atypical lymphocytes (%)	6	0.000	5	0.800	0.474
Platelets (1,000/cmm)	288	-0.594	228	-2.961	0.767

* p-value for the intergroup comparison of adjusted mean values at the final on-drug assessment.

Appendix 8.1.6.3.1.3:
Mean Change from Baseline to Last Visit in Urinalysis Values in Placebo-Controlled Studies (208, 209, and 367)

	Venlafaxine ER		Placebo		p-value*
	Total pts.	Mean change	Total pts.	Mean change	
Urine pH	156	0.019	156	0.045	0.926
Specific gravity	156	0.001	156	0.000	0.218

* p-value for the intergroup comparison of adjusted mean values at the final on-drug assessment.

Appendix 8.1.6.3.2.1: Criteria for Identifying Patients with Potentially Clinically Significant Change in Clinical Chemistry Analytes		
Analyte	Unit	Criteria
Sodium	mEq/L	↑ or ↓ ≥ 5 & ONR*
Potassium	mEq/L	↑ or ↓ ≥ 0.5 & ONR
Calcium	mg/dL	↑ or ↓ ≥ 2 & ONR
Chloride	mEq/L	↑ or ↓ ≥ 5 & ONR
Carbon dioxide	mEq/L	↑ or ↓ ≥ 4 & ONR
BUN	mg/dL	≥ 1.5 x ULN
Creatinine	mg/dL	≥ 1.5 x ULN
Total bilirubin	mg/dL	≥ 1.5 x ULN
ALT/SGPT	IU/L	≥ 3 x ULN
AST/SGOT	IU/L	≥ 3 x ULN
LDH	IU/L	≥ 3 x ULN
Alkaline phosphatase	IU/L	≥ 3 x ULN
Cholesterol	mg/dL	↑ ≥ 50 & ONR
Triglycerides	mg/dL	↑ ≥ 50 & ONR
Glucose	mg/dL	≥ 180 or < 50
Uric acid	mg/dL	↑ of ≥ 3 & ONR
Total protein	g/dL	Change ≥ 1 & ONR
Albumin	g/dL	↓ ≥ 1 & ONR

*ONR=outside normal range.

Appendix 8.1.6.3.2.2: Criteria for Identifying Patients with Potentially Clinically Significant Change in Hematology Analytes		
Analyte	**Unit**	**Criteria**
Hematocrit		↓ ≥ 5%
Hemoglobin	g/dL	↓ ≥ 2
WBC count	cells/mm^3	↑ or ↓ ≥ 2000 & ONR
Platelet count	cells/mm^3	↑ ≥ 20% or ↓ ≥ 20%, & ONR

Appendix 8.1.6.3.2.3: Criteria for Identifying Patients with Potentially Clinically Significant Change in Urinary Analytes	
Analyte	**Criteria**
Protein/albumin	+ or anything not -
Glucose/sugar	+ or anything not -
Hemoglobin/blood	+ or anything not -

Appendix 8.1.6.3.2.4:
Proportions of Patients Having Potentially Clinically Significant Changes in Chemistry Variables in Phase 3 Studies

	PLACEBO-CONTROLLED STUDIES						ALL PHASE 3		
	Venlafaxine ER			Placebo			Venlafaxine ER		
	N	Abnormal #	Abnormal %	N	Abnormal #	Abnormal %	N	Abnormal #	Abnormal %
Sodium-Low	174	0	0	179	0	0	289	2	<1
Potassium-High	174	0	0	178	1	<1	289	0	0
Potassium-Low	174	1	<1	178	1	<1	289	1	<1
Chloride-High	174	1	<1	179	0	0	289	1	<1
BUN-High	144	1	<1	75	0	0	262	2	<1
Tot Bili-High	318	0	0	253	4	2	552	3	<1
ALT/SGPT-High	145	0	0	77	0	0	269	1	<1
Cholesterol-High	320	3	<1	255	4	2	555	12	2
Triglycerides-High	146	7	5	75	2	3	264	21	8
Glucose-High	174	0	0	178	2	1	289	2	<1
Uric acid-High	174	1	<1	180	0	0	290	1	<1
Total protein-High	318	0	0	256	1	<1	551	0	0
Total protein-Low	318	1	<1	256	1	<1	551	2	<1

Appendix 8.1.6.3.2.5:
Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in Phase 3 Studies

	PLACEBO-CONTROLLED STUDIES						ALL PHASE 3		
	Ven ER			Placebo			Ven ER		
	N	Abnormal #	%	N	Abnormal #	%	N	Abnormal #	%
Hemoglobin -Decrease	319	3	<1	253	2	<1	556	8	1
Hematocrit -Decrease	320	13	4	252	14	6	558	23	4
WBC-High	319	10	3	253	9	4	557	20	4
WBC-Low	319	4	1	253	3	1	557	12	<1
Platelets-high	318	3	<1	253	2	<1	555	11	2
Platelets-low	318	2	<1	253	1	<1	555	3	<1

Appendix 8.1.6.3.2.6:
Proportions of Patients Having Potentially Clinically Significant Changes in Urinalysis Variables in Phase 3 Studies

	PLACEBO-CONTROLLED STUDIES						ALL PHASE 3		
	Venlafaxine ER			Placebo			Venlafaxine ER		
	N	Abnormal #	%	N	Abnormal #	%	N	Abnormal #	%
Protein/ albumin	172	15	9	176	10	6	287	34	12
Glucose	172	1	<1	176	3	2	287	6	2
Blood	174	22	13	179	19	11	289	58	20

Appendix 8.1.7.1: Vital Sign Assessment in the Integrated Safety Database Studies		
Study	**Measurements**	**Frequency**
208	Supine pulse Supine and standing BP Oral temperature Weight	Baseline and study weeks 1, 2, 3, 4, 6, 8, and 12
209	Supine pulse Supine and standing BP Oral temperature Weight	Baseline and study weeks 1, 2, 3, 4, 6, and 8
367	Supine pulse Supine and standing BP Weight	Baseline and study weeks 1, 2, 4, 6, and 8
365	Supine pulse Supine and standing BP (Postural BP Change) Weight	Baseline and months 0.5, 1, 2, 4, 6, 8, 10, and 12
369	Supine pulse Supine and standing BP Oral temperature	Baseline and study days 14, 28, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360
	Weight	Baseline and study days 28, 90, 180, 270, and 360

APPENDIX 8.1.7.3.1:
Mean Change from Baseline in Vital Sign Measures
(Studies 208, 209, and 367)

Measure	VEN ER		PLACEBO		p-value *
	N	Mean Δ	N	Mean Δ	
Systolic BP (Standing) (mmHg)	345	+0.287	281	-0.389	0.130
Diastolic BP (Standing) (mmHg)	345	+1.438	281	-0.071	0.016
Systolic BP (Supine) (mmHg)	343	+0.468	280	-0.884	0.034
Diastolic BP (Supine) (mmHg)	343	+1.206	280	-0.176	0.009
Pulse (Supine) (bpm)	343	+1.549	280	+1.040	0.146
Temperature (Oral) (^{0}F)	170	+0.040	176	+0.060	0.886
Weight (lbs)	345	-1.151	280	+1.020	<0.001

* p-value for the intergroup comparison of adjusted means at the final on-drug assessment.

APPENDIX 8.1.7.3.2.1: Criteria for Identifying Vital Sign Changes of Potential Clinical Significance	
Variable	**Criteria**
Systolic Blood Pressure	Increase of ≥20 mmHg and BP≥180mmHg OR Decrease of ≥20mmHg and BP≤90mmHg
Diastolic Blood Pressure	Increase of ≥15 mmHg and BP≥105mmHg OR Decrease of ≥15mmHg and BP≤50mmHg
Pulse	Increase of ≥15 bpm and rate≥120 bpm OR Decrease of ≥15 bpm and rate≤50 bpm
Postural BP Change	Decrease of ≥25mmHg systolic OR ≥10mmHg diastolic when going from supine to standing
Temperature	Increase of ≥2°F and temperature ≥101°F
Weight	Change of ≥7% in body weight

APPENDIX 8.1.7.3.2.2:
Proportions of Patients with Vital Sign Changes of Potential Clinical Significance

	Short-term, placebo-controlled studies						Phase 3		
	VEN ER			PLACEBO			VEN ER		
	N	Abnormal		N	Abnormal		N*	Abnormal	
		#	%		#	%		#	%
↑ SBP (standing)	354	0	0	282	1	<1	719	4	<1
↓ SBP (standing)	354	7	2	282	7	3	719	14	2
↑ DBP (standing)	354	7	2	282	5	2	719	22	3
↓ DBP (standing)	354	2	<1	282	2	<1	719	12	2
↑ SBP (supine)	354	3	<1	282	0	0	719	7	<1
↓ SBP (supine)	354	9	3	282	6	2	719	12	2
↑ DBP (supine)	354	7	2	282	1	<1	719	17	2
↓ DBP (supine)	354	6	2	282	6	2	719	13	2
↑ pulse (supine)	354	0	0	282	0	0	719	2	<1
↓ pulse (supine)	354	0	0	282	1	<1	719	0	0
↓ SBP with postural Δ	354	21	6	282	27	10	719	53	7
↓ DBP with postural Δ	354	112	32	282	69	25	719	257	36
↑ Weight	354	12	3	282	3	1	717	33	5
↓ Weight	354	6	2	282	6	2	717	37	5

* Phase 3 denominators were not corrected for venlafaxine ER patients who participated in both short- and long-term studies; corrected fractions would be slightly higher.

Appendix 8.1.8.1: Schedule for ECG Recording in Phase 3 Studies	
Study	Frequency
208	Pre-study and week 12
209	Pre-study and week 8
367	Pre-study and week 8
365	Screening and months 6 and 12
369	Pre-study and days 28, 90, 180, 270, & 360

Appendix 8.1.8.3.1:
Mean Change from Baseline to Last Visit in ECG Parameters in Placebo-Controlled Studies (208, 209, and 367)

	Venlafaxine ER		Placebo		p-value*
	N	Mean change	N	Mean change	
PR interval (msec)	275	-1.693	220	+3.541	0.002
QRS interval (msec)	273	-0.905	219	-0.950	0.820
QTc interval (msec)	275	+4.730	220	-1.896	0.033
QT interval (msec)	195	-2.426	132	-1.515	0.735
Heart rate (bpm)	277	+3.993	220	+0.889	<0.001

* Based on the intergroup comparison of adjusted means at the final on-drug assessment.

Appendix 8.1.8.3.2.1: Criteria for Determining Potentially Clinically Significant Changes in ECG Results*	
Variable	Criteria
PR interval	Increase ≥ 10% and >200 msec
QRS interval	≥ 120 msec
QT_c	Increase ≥ 10% and > 440 msec
Rhythm	Change from prior normal rhythm to abnormal

* All changes are from baseline unless otherwise noted.

Appendix 8.1.8.3.2.2: Phase 3 Depression Studies: Proportions of Patients with ECG Changes of Potential Clinical Significance								
	PLACEBO-CONTROLLED STUDIES						ALL PHASE III		
	Venlafaxine ER			Placebo			Venlafaxine ER		
	N	Abnormal #	%	N	Abnormal #	%	N	Abnormal #	%
PR interval	312	0	0	252	2	<1	552	1	<1
QRS interval	313	7	2	252	5	2	553	11	2
QTc interval	313	13	4	252	3	1	553	30	5
Rhythm	314	4	1	252	3	1	555	12	2