CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-104

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	22-104
Drug:	Venlafaxine Extended Release Tablets
Strengths:	37.5 mg, 75 mg, 150 mg and 225 mg
Sponsor:	Osmotica Pharmaceutical
Indication:	Treatment of Major Depressive Disorder Treatment of Social Anxiety Disorder
Submission Type:	Response to Approvable letter
Submission Date:	12/28/08
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

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1. Executive Summary

1.1. Recommendations

It is recommended that the sponsor adopt the following dissolution method and specification for Venlafaxine 37.5 mg, 75 mg, 150 mg and 225 mg Extended Release Tablets.

Method

Apparatus:	*USP Apparatus II (Paddle)*
Speed:	*50 rpm*
Media:	*Water at 37°C*
Volume:	*900 mL*

Specification: Q at

4 hour	
12 hour	
20 hour	*NLT*

1.2. Summary of Biopharmaceutics Findings

Background: The sponsor submitted a response to an approvable (AE) letter issued 10/4/07 for Venlafaxine Extended Release Tablets. In the AE letter, the sponsor was requested to accept the dissolution method and specification proposed by the Agency. It was noted in the AE letter that the IVIVC submitted in the original application was not acceptable and additional information was requested from the sponsor. However, this additional data requested was not a condition of approval of the product. The sponsor stated in their response to the AE letter that they will address the IVIVC issue post approval. The following is the dissolution method and specification proposed by the Agency that was included in the AE letter.

FDA Proposal for Venlafaxine 37.5 mg, 75 mg, 150 mg, and 225 mg

Method

Apparatus:	*USP Apparatus II (Paddle)*
Speed:	*50 rpm*
Media:	*Water at 37°C*
Volume:	*900 mL*

Specification: Q at

4 hour	
12 hour	
20 hour	*NLT*

The sponsor accepted the proposed method but suggested a different specification. The Sponsor proposed to have different specifications for the 37.5 mg relative to the 75 mg, 150 mg and 225 mg strengths. The following are the specifications for the 37.5 mg and the higher strengths proposed by the sponsor.

Time	*37.5 mg*	*75 mg, 150 mg and 225 mg*
4 hour		
12 hour		
20 hour	*NLT* —	*NLT* —

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The sponsor's rationale for these new specifications was that the 37.5 mg tablet core has approximately — f the drug load —) compared to the higher strengths. This was done in order to achieve a pharmaceutically elegant product. The excipient used to augment the Venlafaxine — provide a larger tablet weight for the 37.5 mg product was —. According to the sponsor, — s water insoluble material that is significantly different from the highly soluble Venlafaxine. As such, there is a lag time required to have the full effect of the osmotic pump causing the release of the Venlafaxine from the device which is somewhat longer for the 37.5 mg product compared to the higher strengths (for example: respectively, for the 75 mg and 225 mg lots). The *in vitro* release difference was not reflected in an in vivo bioavailability difference. The 37.5 mg product is bioequivalent to the equivalent strength of Effexor XR as are the higher strengths.

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Comments: After review of the dissolution profiles of the bio-lots for each dosage strength, it was observed that the behavior of the release characteristics are comparable between the dosage strengths. The major discrepancy in the bio-lots meeting the Agency or Sponsor's proposed dissolution specifications was in the 150 mg not the 37.5 mg tablet strength. Three (3) tablets from the bio-lot for the 150 mg failed to meet the sponsor's specification and two were at borderline of the dissolution specification. Two tablets from the 150 mg bio-lot failed to meet the Agency's specification. All tablets from all the bio-lots pass USP L2 requirements under both the Sponsor's and Agency's specification scenarios. It is not anticipated that the Agency's proposed specification would result in significant batches failing the dissolution specification. It is preferable and highly recommended to have one dissolution specification set for a particular drug product. Therefore, it is recommended that the sponsor adopt the Agency's proposed dissolution specifications for all Venlafaxine Extended Release tablets. The sponsor's proposal of two specifications for Venlafaxine Extended Release Tablets is not acceptable.

2. Labeling Comments

Edits to the OCP sections of label is included in the PLR under appendix

3. Appendices

Individual Dissolution Data for Bio-lots

PLR

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Kofi Kumi
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Raman Baweja
2/11/2008 02:09:05 PM
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Clinical Pharmacology and Biopharmaceutics Review

NDA:	22104
Generic Name:	Venlafaxine Extended Release
Brand Name:	TBD
Strength and Dosage Form:	37.5 mg, 75 mg, 150 mg, 225 mg Tablets
Indication:	Treatment of Major Depressive Disorder Treatment of Social Anxiety Disorder
Sponsor:	Osmotica Pharmaceutical
Submission Type:	Original NDA (505b(2))
Submission Dates:	12/11/06, 1/31/07, 6/28/07
OCP Division:	DCP 1 (HFD-860)
OND Division:	DPP (HFD-130)
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

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1. Executive Summary

1.1 Recommendations

a) The Office of Clinical Pharmacology (OCP) has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-104 and finds the data acceptable. OCP supports approval of Venlafaxine Extended Release Tablets by Osmotica Pharmaceuticals. Venlafaxine Extended Release Tablets (Osmotica) 37.5, 75 and 225 mg are bioequivalent to an equivalent dose of the approved product, Effexor XR (Wyeth).

b) It is recommended that a waiver of bioequivalence study be granted for the 150 mg Venlafaxine Extended Release Tablet (Osmotica).

c) The following dissolution method and specification are recommended for Venlafaxine Extended Release Tablets (Osmotica)

Apparatus:	*USP Apparatus II (Paddle)*
Speed:	*50 rpm*
Media:	*Water at 37°C*
Volume:	*900 mL*

Specification: Q at

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4 hours:	
12 hours	
20 hours	*NL?*

d) The in vitro in vivo (IVIVC) model developed is not acceptable at this time. It is recommended that sponsor consult the Agency's Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of IVIVC and submit the required data (e.g. details of model development including equations, data sets, and control files) for review in a future submission. The guidance can be found at http://www.fda.gov/cder/guidance/index.htm.

1.2 Phase IV Recommendation

The sponsor should conduct studies to investigate dose-dumping in the presence of alcohol. The sponsor should perform dissolution studies for all Venlafaxine Extended Release strengths using the accepted dissolution conditions with the addition of (of ethanol to the dissolution media. The accepted dissolution method is:

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Apparatus:	USP Apparatus II (Paddle)
Speed:	50 rpm
Media:	Water at 37°C
Volume:	900 mL

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Regulatory Background: The application was filed as a 505(b)(2) NDA with the clinical, preclinical and some of the pharmacokinetic data referenced to Effexor XR™ (NDA 20699) which is approved. Safety and efficacy are based on the data found in NDA 20699 for Effexor XR® Capsules. The sponsor is seeking approval for Venlafaxine Extended-release Tablets 37.5 mg, 75 mg, 150 mg and 225 mg. The basis for the request for approval is the demonstration of bioequivalence of the Venlafaxine Extended-Release Tablets to the equivalent dose of Effexor XR® Capsules. Effexor XR is recommended to be taken with food. The sponsor is seeking a waiver of bioequivalence study for the 150 mg Venlafaxine Extended Release Tablets.

Therapeutic indication and Dosage Regimen: The sponsor is seeking approval of Venlafaxine Extended Release Tablets for the treatment of Major Depressive Disorder and Social Anxiety Disorder. Effexor XR is approved for these indications. For most patients, the recommended starting dose for Venlafaxine hydrochloride extended release tablets is 75 mg/day administered in a single dose. For some patients, it may be necessary to start 37.5 mg/day. Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day.

Bioequivalence of Venlafaxine Extended Release Tablets and Effexor XR Capsules:

Venlafaxine 225 mg extended release tablet (highest strength; Osmotica) was demonstrated to be bioequivalent to Effexor 225 (150 + 75) mg XR capsules after a single dose administration under fed conditions.

Venlafaxine ER Tablets 37.5 mg formulation (Osmotica) was bioequivalent to Effexor® XR (Venlafaxine HCl, Wyeth) 37.5 mg Extended-Release Capsules when administered under fed and fasting conditions.

Venlafaxine HCl 75 mg Extended Release Tablets (Osmotica) was demonstrated to be bioequivalent to Effexor XR 75 mg Capsules when administered under fed conditions. But Venlafaxine ER 75 mg tablets were not bioequivalent to Effexor XR 75 mg under fasting conditions. The 90% confidence intervals (CI) for AUC and Cmax of Venlafaxine under fasting conditions were 106.86% – 120.71% and 113.07% – 126.10%, respectively. The regulatory criteria for bioequivalence is for the 90% CI for AUC and Cmax to fall within an interval of 80% - 125%. Venlafaxine Extended release tablets are recommended to be taken with food. But if the 75 mg tablet is taken under fasting conditions, the difference in the 90% CI for Cmax is not expected to be clinically relevant.

Bio-Waiver of 150 mg Venlafaxine Extended Release Tablets (Osmotica)

The sponsor demonstrated that Venlafaxine Hydrochloride Extended-release Tablets 75 mg and Effexor XR 75 mg Capsules were bioequivalent under fed conditions. Additionally, the sponsor demonstrated that Venlafaxine Hydrochloride Extended release Tablets 225 mg and Effexor XR 75 mg + 150 mg were bioequivalent under fed conditions. The 75 mg, 150 mg, and 225 mg are compositionally proportional. And the

dissolution profiles of the 75 mg, 150 mg and 225 mg venlafaxine extended release tablets were similar (f2 >50). Therefore, a waiver of bioequivalence study for the 150 mg Venlafaxine Extended Release Tablet is justified and recommended.

In Vitro In Vivo Correlation (IVIVC): The IVIVC is not acceptable at this time.

Dissolution: The dissolution method proposed by the sponsor is acceptable. But the following specification proposed by the sponsor is not acceptable.

4 hours: [redacted]
12 hours [redacted]
20 hours: NLT [redacted]

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OCP recommends that the method proposed by the sponsor but with the following specification for Venlafaxine Extended Release Tablets (Osmotica), 37.5 mg, 75 mg, 150 mg, and 225 mg strengths, be adopted.

Apparatus:	*USP Apparatus II (Paddle)*
Speed:	*50 rpm*
Media:	*Water*
Volume:	*900 mL*

Specification: Q at

4 hours: [redacted]
12 hours
20 hours *NLT* [redacted]

b(4)

These specifications are based on the dissolution profiles of the lots used in the bioequivalence studies.

2. Question Based Review (QBR)

The QBR section of the review has used a deductive approach (i.e. starts with conclusions followed with supportive details) as instructed by CDER Review Template MaPP 4000.4.

2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The NDA was filed as a 505(b)(2) with the clinical, preclinical and some of the pharmacokinetic data referenced to the innovator, Effexor XR™ (NDA 20699). This method of filing was agreed to by the Agency.

The NDA is for Venlafaxine Extended-release Tablets 37.5 mg, 75 mg, 150 mg and 225 mg. Clinical safety and efficacy are based on the data found in NDA 20699 for Effexor XR® Capsules. The basis for this reference is the demonstration of bioequivalence of the

Venlafaxine Extended-Release Tablets 37.5 mg and 75 mg to the equivalent strengths of Effexor XR® Capsules and of the Venlafaxine Extended-release Tablets 225 mg to one Effexor XR® Capsules 75mg combined with one Effexor XR® Capsules 150 mg.

2.1.1. What is the proposed therapeutic indication for Venlafaxine Extended Release Tablet?

Venlafaxine extended release tablets is indicated for the treatment of major depressive disorder and social anxiety disorder

2.1.2. What are the proposed dosage and route of administration?

The proposed dosing regimen is similar to that for the approved Effexor XR: For most patients, the recommended starting dose for venlafaxine hydrochloride extended release tablets is 75 mg/day administered in a single dose. For some patients, it may be necessary to start at 37.5 mg/day. Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day.

Venlafaxine extended release tablets are intended to be taken orally. Venlafaxine is recommended to be taken with food.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1. What are the design features of the bioequivalence studies used to support dosing or claims?

In the approved labeling of Effexor XR® it was noted that in short-term placebo controlled clinical trials in patients with major depressive disorder, the incidence of nausea for Effexor XR® was reported in 31% of patients. This was the highest reported adverse event incidence. Therefore, the approved labeling of Effexor XR® recommends that the product be dosed only with food. The bioequivalence for the highest strength of venlafaxine extended release tablets were conducted under fed conditions.

The type of bioequivalence studies which were performed to support the claims and dosing regimen are listed below and were based on the following: proportionality of three (75, 150, 225 mg) of the four strengths, the fact that the product is recommended to be dosed with food in clinical use, the desire to not dose the highest strength in a fasted state due to the incidence of nausea and determine the behavior of Venlafaxine Extended Release Tablets when lower doses are dosed in the fasted state.

Two 4-way Crossover Single-Dose Studies in Fed and Fasted Condition

37.5 mg Venlafaxine Extended-release tablet compared to 37.5 mg Effexor XR Capsule (Protocol No. 10672001).
75 mg Venlafaxine Extended Release Tablet compared to 75 mg Effexor XR Capsule (Protocol No. 10572001).

The studies were single-dose, randomized, four-period crossover bioequivalence study under fed and fasting conditions. The products compared were Venlafaxine Extended-release Tablets 37.5 mg and Effexor XR® Capsules 37.5 mg. And, Venlafaxine Extended-release Tablets 75 mg and Effexor XR® Capsules 75 mg.

One 2-way Crossover Single Dose Study in Fed Condition (Protocol No. R04-0776)

The study was a single-dose, randomized, two-period crossover bioequivalence study under fed conditions. The products compared were Venlafaxine Extended-release Tablets 225 mg and Effexor XR® Capsules 75 mg plus Effexor XR® Capsules 150 mg.

One 2-way Multiple Dose, Randomized, 2-Period, Crossover Study in Fed Condition (Protocol No. R04-778)

225 mg Venlafaxine Hydrochloride Extended-release Tablets compared to the combination of one 75 mg Effexor XR Capsule and one 150 mg Effexor XR Capsule administered daily for 7 days.

The sponsor is seeking a waiver of a bioequivalence study for Venlafaxine 150 mg extended release tablet.

2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moieties in the plasma have been adequately identified and measured (Refer to section on Analytical Methods).

2.2.3. Exposures

2.2.3.1. Are the exposures after administration of 225 mg Venlafaxine Extended Release Tablets (Osmotica) similar to an equivalent dose of the approved Venlafaxine Extended Release Capsule (Effexor XR)?

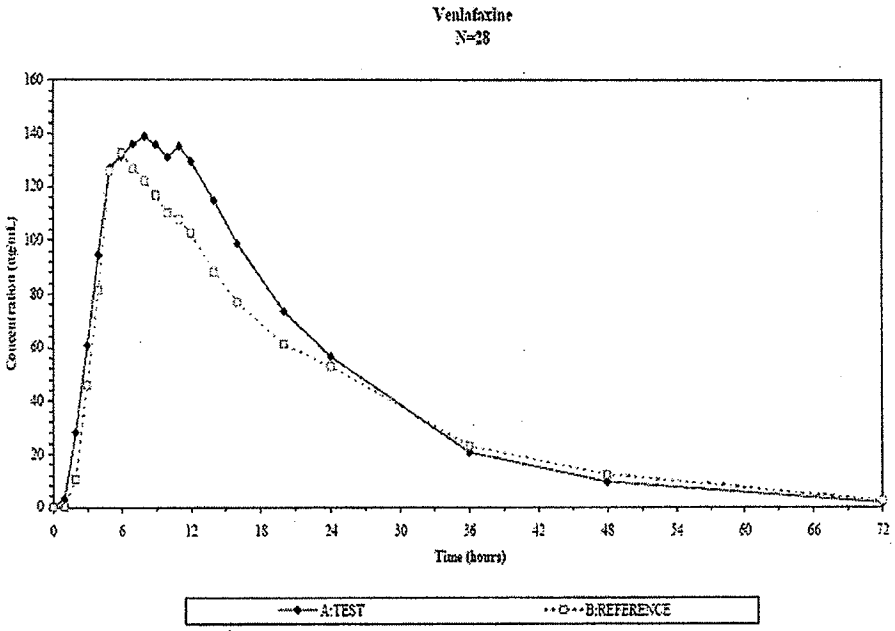
Venlafaxine 225 mg extended release tablet was demonstrated to be bioequivalent to Effexor 225 (150 + 75) mg XR capsules after a single dose administration under fed conditions. The approved venlafaxine extended release capsules (Effexor XR) is recommended to be taken with food.

The sponsor conducted a study to compare the relative bioavailability (rate and extent of absorption) of Venlafaxine Hydrochloride Extended Release (ER) Tablets 225 mg by Osmotica Pharmaceutical Corp. with that of the approved Effexor XR® (venlafaxine extended release, Wyeth) Capsules 225 mg (150 mg plus 75 mg) following a single, oral dose administration to healthy, adult subjects under fed conditions.

The study was a single-center, randomized, two-way crossover trial conducted under fed conditions. On study day 1, each subject received either a single, oral dose of the test

product, Venlafaxine ER (Osmotica) Tablet 225 mg, or a single, combined oral dose of the reference product, Effexor XR® Extended-Release Capsules 150 mg and 75 mg. Dosing occurred 30minutes after the initiation of a standardized, high fat breakfast preceded by an overnight fast. Following a seven day washout period, subjects were dosed with the alternative treatment as per the randomization. The following figure depicts the plasma profiles for the test and reference products.

Figure 1: Mean Plasma Concentration (0- 72 hrs) Profile after Administration of Test and Reference Products



The following table contains the results of the analysis

Table 1

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Venlafaxine N=28				
Parameter	**Test**	**Reference**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	2343.99	2137.48	109.66	(103.8, 115.85)
AUC_{0-inf} (ng-hr/mL)	2431.98	2254.30	107.88	(102.64, 113.39)
C_{max} (ng/mL)	132.34	130.42	101.47	(94.15, 109.37)

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax

The 90% confidence interval was contained within the regulatory criteria of 80 % to 125%.

Recalculation by the Reviewer after dropping subjects per DSI Inspection Report

The above study was inspected by the Division of Scientific Investigation (DSI). DSI stated that the subject sample concentrations in runs —— cannot be assured. These runs affected the venlafaxine concentration for subjects 15, 16, 18 and 20. Therefore, DSI recommended that the data for these patients should not be considered for bioequivalence. The reviewer recalculated the bioequivalence of the two formulations both with and without subjects 15, 16, 18 and 20. The results of the reviewer's calculations are provided below. The data was Ln transformed prior to the statistical analysis

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Table 2

Geometric Means, Ratio of Means and 90% Confidence Intervals Venlafaxine (n=28)				
Parameter	Test	Reference	% Ratio	90% CI
AUC (0-t) (ng*hr/mL)	2343.99	2137.48	109.66	103.79 – 115.85
AUC (0-∞) (ng*hr/mL)	2431.98	2254.30	107.88	102.63– 113.39
Cmax (ng/mL)	132.34	130.42	101.47	94.15 – 109.37

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax

Table 3

Geometric Mean, Ratio of Means and 90% Confidence Intervals Venlafaxine (n=24) (Without subjects 15, 16, 18 and 20)				
Parameter	Test	Reference	% Ratio	90% CI
AUC (0-t) (ng*hr/mL)	2364.95	2169.12	109.03	102.55 – 115.91
AUC (0-∞) (ng*hr/mL)	2454.82	2290.04	107.19	101.46 – 113.26
Cmax (ng/mL)	135.66	130.13	104.24	96.27 – 112.88

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax

The results of the recalculation including all subjects are the same as that obtained by the sponsor. The results of the recalculation without subjects 15, 16, 18 and 20 are contained in Table 3 above. The recalculated 90% CI indicated that 225 mg venlafaxine extended release tablets (Osmotica) are bioequivalent to 225 mg Effexor XR capsule dose.

The following table contains the statistical analysis for the active metabolite, O-desmethyl venlafaxine. The results for the metabolite were not considered in determination of bioequivalence between Venlafaxine Extended Release Tablets (Osmotica) and Effexor XR. However, the 90% CI were contained within the 80% to 125% criteria for bioequivalence.

Table 4

Geometric Means, Ratio of Means and 90% Confidence Intervals Desmethylvenlafaxine (n=28)				
Parameter	Test	Reference	% Ratio	90% CI
AUC (0-t) (ng*hr/mL)	9910.07	9004.41	110.06	106.35 – 113.89
AUC (0-∞) (ng*hr/mL)	10204.96	9507.14	107.34	103.83 – 110.97
Cmax (ng/mL)	341.95	289.28	118.21	112.49 – 124.21

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax

2.2.3.2. Are the exposures after administration of 37.5 mg Venlafaxine Extended Release (Osmotica) similar to an equivalent dose of the approved Venlafaxine Extended Release Capsule (Effexor XR)?

Venlafaxine ER Tablets 37.5 mg formulation (Osmotica) was bioequivalent to Effexor® XR (Venlafaxine HCl, Wyeth) 37.5 mg Extended-Release Capsules after administration under both fasting and fed conditions.

The sponsor conducted a study to evaluate the bioequivalence of Osmotica Venlafaxine HCl 37.5 mg extended release tablets (Osmotica) compared to Effexor® XR (venlafaxine hydrochloride) 37.5 mg extended-release capsules (Wyeth) under fasted and fed conditions in healthy adult subjects.

The study was a randomized, single-dose, four-period, crossover study under fasting and fed conditions comparing equal doses of the test and reference products. In each study period, a single 37.5 mg dose was administered to all subjects following an overnight fast or following a standardized breakfast which was preceded by an overnight fast. The test formulation was Venlafaxine ER Tablets 37.5 mg (Osmotica) and the reference formulation was Venlafaxine HCl Extended-Release Capsules (Effexor XR, Wyeth). The subjects received the test product in two study periods and the reference product in the other two study periods; the order of administration was according to the dosing randomization schedule. The treatments administered were Treatment A: Venlafaxine HCl 37.5 mg ER Fasted, Treatment B: Venlafaxine HCl 37.5 mg ER Fed, Treatment C: Effexor XR 37.5 mg Fasted and Treatment D: Effexor XR 37.5 mg Fed. There was a 7-day interval between treatments. The following table contains the results of the bioequivalence evaluation.

Table 5: Comparison of Venlafaxine HCl 37.5 mg Fasted (Treatment A) vs Effexor XR 37.5 mg Fasted (Treatment C)

PK Parameter	Treatment A (N=36)	Treatment C (N=35)	Ratio (A/C)	90% Confidence Interval
ln AUC(0-inf)	431.73	405.80	1.0639	100.31, 112.85
ln AUC(0-t)	365.59	351.14	1.0411	97.58, 111.09
ln Cmax	24.7648	24.4327	1.0136	95.58, 107.48

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax. The units for AUCs are ng*hr/mL and Cmax are ng/mL.

Table 6: Comparison of Venlafaxine HCl 37.5 mg Fed (Treatment B) vs Effexor XR 37.5 mg Fed (Treatment D).

PK Parameter	Treatment B (N=35)	Treatment D (N=35)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	449.12	426.73	1.0525	98.98, 111.91
ln AUC(0-t)	370.04	370.71	0.9982	93.49, 106.58
ln Cmax	24.4170	27.3110	0.8940	84.26, 94.86

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax. The units of AUCs are ng*hr/mL and Cmax are ng/mL.

Statistical comparison of test and reference treatment under fed and fasted conditions resulted in 90% CI within the recommended range of 80-125% for the ratio of means for AUC(0-inf), AUC(0-t) and Cmax.

The following table contains the statistical analysis for the active metabolite, O-desmethyl venlafaxine. The results for the metabolite were not considered in determination of bioequivalence between Venlafaxine Extended Release Tablets (Osmotica) and Effexor XR; the 90% CI for AUC and Cmax are contained within 80 – 125%.

Table 7: Comparison of Desmethylvenlafaxine after administration of Venlafaxine Extended Release Tablet 37.5 mg Fed (Treatment B) vs Effexor XR 37.5 mg Fed (Treatment D).

PK Parameter	Treatment B (N=35)	Treatment D (N=35)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	1377.66	1373.70	1.0029	96.32, 104.41
ln AUC(0-t)	1243.57	1238.81	1.0038	96.36, 104.58
ln Cmax	41.7673	42.3271	0.9868	94.90, 102.60

Results are back transformed from results of ANOVA models using natural logarithms for AUC_{0-inf}, AUC_{0-t} and C_{max}

The units of AUCs are ng*hr/mL and Cmax are ng/mL.

2.2.3.3. Are the exposures after administration of 75 mg Venlafaxine Extended Release (Osmotica) similar to an equivalent dose of the approved Venlafaxine Extended Release Capsule (Effexor XR)?

Venlafaxine HCl 75 mg Extended Release Tablets (Osmotica) was demonstrated to be bioequivalent to Effexor XR 75 mg when administered under fed conditions. However, when administered under fasting conditions, the two formulations were not bioequivalent. The approved Effexor XR is recommended to be taken with food.

The sponsor conducted a study to evaluate the bioequivalence of Venlafaxine HCl 75 mg extended release tablets (Osmotica) to Effexor XR (Venlafaxine hydrochloride) 75 mg

extended release capsules (Wyeth) under fasted and fed conditions in healthy adult subjects

The study was a randomized, single-dose, four-period, crossover trial under fasting and fed conditions comparing equal doses of the test and reference products. Subjects were randomized to one of four sequences. A single dose of 75 mg venlafaxine was administered in each study period. The test formulation was Venlafaxine ER Tablets 75 mg (Osmotica), and the reference formulation was Effexor XR (Venlafaxine HCl) Extended-Release Capsules (Wyeth). The subjects received the test product in two study periods and the reference product in the other two study periods. The test/reference products were administered after an overnight fast of at least 10 hours and following a standardized high-fat breakfast which was preceded by an overnight fast of at least 10 hours. There was a 7-day interval between treatments.

The following tables contain the results of the statistical analysis to determine bioequivalence.

Table 8: Comparison of Venlafaxine HCl 75 mg Fasted (Treatment A) vs Effexor XR 75 mg Fasted (Treatment C)

PK Parameter	Treatment A (N=31)	Treatment C (N=30)	Ratio (A/C)	90% Confidence Interval
ln AUC(0-inf)	705.20	620.90	1.1358	106.86, 120.71
ln AUC(0-t)	649.48	552.04	1.1765	111.11, 124.57
ln Cmax	43.5372	38.4611	1.1941	113.07, 126.10

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax. The units for AUCs are ng*hr/mL and Cmax are ng/mL.

Table 9: Comparison of Venlafaxine HCl 75 mg Fed (Treatment B) vs Effexor XR 75 mg Fed (Treatment D)

PK Parameter	Treatment B (N=31)	Treatment D (N=31)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	702.90	696.28	1.0095	95.05, 107.21
ln AUC(0-t)	637.75	622.28	1.0249	96.80, 108.50
ln Cmax	42.4712	44.4441	0.9556	90.50, 100.90

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax. The units for AUCs are ng*hr/mL and Cmax are ng/mL.

The 90% confidence intervals for the ratios of means for both log transformed Cmax, AUC after administration under fed conditions were within the stipulated range of 80% to 125%.

Statistical comparisons of ln-transformed AUC(0-inf) and AUC(0-t), for the test treatment vs. reference treatment under fasted conditions, resulted in 90% confidence intervals (CI) for the ratios of means within the stipulated range of 80-125%. However, the 90% CI for Cmax was above the stipulated range of 80-125% with an interval of (113.1, 126.1).

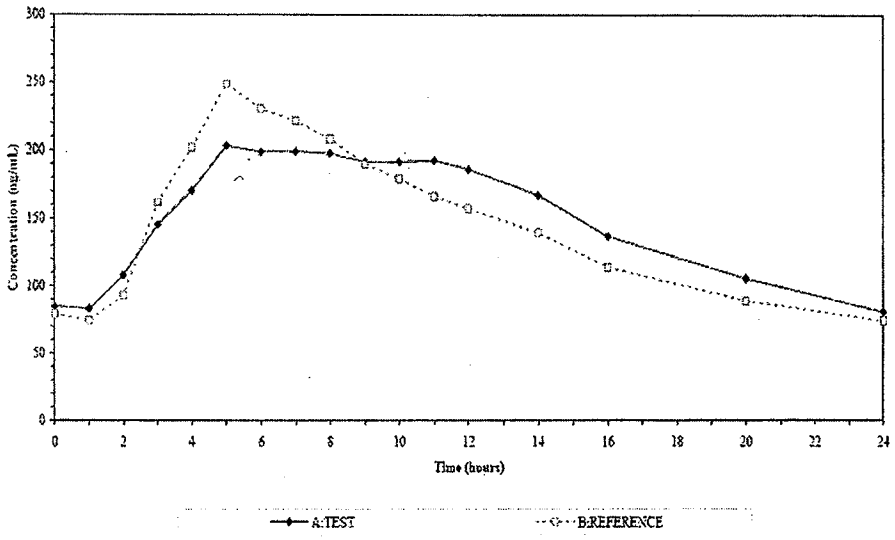
2.2.3.4. Are the exposures to venlafaxine after multiple dose administration of 225 mg Venlafaxine Extended Release (Osmotica) similar to that from an equivalent dose of the approved Venlafaxine Extended Release Capsule (Effexor XR)?

The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean for AUC and Cmax were within the 80% to 125% limits. Therefore, 225 mg Venlafaxine Extended Release (Osmotica) was demonstrated to be bioequivalent to 225 mg Effexor XR (Wyeth) after multiple dose administration.

The sponsor conducted a study that compared the relative bioavailability (rate and extent of absorption) of 225 mg Venlafaxine Hydrochloride Extended-Release Tablets (Osmotica) with that of 225 mg (1 × 150 mg and 1 × 75 mg) Effexor XR Capsules (Wyeth) following multiple oral doses in healthy adult volunteers.

The study was a multiple dose, randomized, two-period, two-treatment, two-sequence, crossover trial comparing equal doses of test and reference products. In each study period, seven 225 mg doses were administered to all subjects following the completion of a standardized high fat breakfast 30 minutes prior to dosing every 24 hours for the duration of the study period (7 days). The test formulation was 225 mg Venlafaxine Hydrochloride Extended-Release Tablet (Osmotica) and the reference formulation was Effexor® XR Capsules (venlafaxine hydrochloride). The subjects received the test product in one study period and the reference product in the other study period. There was a 7 day washout interval between treatments.

Figure 2: Mean Plasma Concentration (0 – 24 hours) profile for Venlafaxine after administration of Test and Reference Products



The following table summarizes the result of the analyses performed on the pharmacokinetic parameters for the test and reference products and the 90% confidence intervals.

Table 10

Geometric Means, Ratio of Means, and 90% Confidence Intervals Venlafaxine Ln-Transformed Data N=33				
Parameter	Test	Reference	% Ratio	90% CI
AUC_{0-t} (ng-hr/mL)	3093.33	2939.84	105.22	(101.16, 109.45)
C_{max} (ng/mL)	198.02	231.73	85.45	(82.26, 88.77)

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax.

The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean are within the 80% and 125% limits for C_{max} and AUC_{0-t} of the ln-transformed data.

2.2.3.5. Has the sponsor provided sufficient justification for a biowaiver of bioequivalence study for the 150 mg strength?

Yes the sponsor has provided sufficient justification to grant a waiver of bioequivalence study for the 150 mg venlafaxine extended release tablet (Osmotica). Therefore, the reviewer recommends a waiver of a bioequivalence study for the 150 mg tablet.

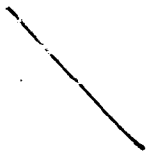
a) The sponsor demonstrated that the same strength of Venlafaxine Hydrochloride Extended-release Tablets 75 mg (Osmotica) and Effexor XR 75 mg were bioequivalent under fed conditions; the approved Effexor XR is recommended to be administered under fed conditions. Additionally, they demonstrated bioequivalence of Venlafaxine Hydrochloride Extended release Tablets 225 mg (Osmotica) and Effexor XR 75 mg + 150 mg under fed conditions.

b) The 75 mg, 150 mg, and 225 mg are compositionally proportional. The sponsor stated that the products are all manufactured with the same formulation and manufacturing process. All strengths are an osmotic tablet in which a tablet core is produced by conventional [redacted] The [redacted] for all strengths is reported to be identical. The composition of the semi-permeable membrane coating solution used to spray onto the tablet cores is qualitatively similar for each strength. The following is the unit composition of the core tablets.

b(4)

Table 11: Unit Composition of the Core Tablets

Component	75 mg (mg/tablet)	150 mg (mg/tablet)	225 mg (mg/tablet)



b(4)

c) The dissolution profiles of the 75 mg, 150 mg and 225 mg Venlafaxine Extended Release Tablets are similar (f2> 50). The similarities in profiles were demonstrated in 4 media (Refer to dissolution section). An illustration of comparable dissolution in the medium of choice, water, is shown in the following figure.

Figure 3: Dissolution Profiles for Venlafaxine Extended Release Tablets

b(4)

2.2.3.6. What are the Pharmacokinetic characteristics of the drug and its major metabolite after administration Venlafaxine Extended Release Tablets (Osmotica)?

This is a 505 b(2) application, hence the pharmacokinetic information for venlafaxine and its metabolite, O desvenlafaxine is by reference to the original application for Venlafaxine Extended Release Capsules (Effexor XR, NDA 20699).

2.3. Biopharmaceutics

2.3.1. What is the Quantitative and Qualitative Composition of Venlafaxine Extended Release Tablets (Osmotica) Formulation?

The following table provides the quantitative and qualitative composition of venlafaxine extended release formulations

Table 12: Venlafaxine 37.5, 75, 150 and 225 mg ER Tablets

Composition	Functionality	37.5 mg dose (mg)	75 mg dose (mg)	150 mg dose (mg)	225 mg dose (mg)

b(4)

The composition of venlafaxine 75, 150 and 225 mg extended release tablets are compositionally proportional. However, the composition of the lowest strength, 37.5 mg venlafaxine extended release tablets is not proportional to the 75, 150 and 225 mg extended release tablets.

2.3.2. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The absorption of venlafaxine after administration of Venlafaxine Extended Release Tablets is not affected by a high fat meal. However, it is reported that there is an increase in side effect (nausea) when Venlafaxine is administered on an empty stomach. Therefore, it is recommended that Venlafaxine Extended Release Tablets be administered with food similar to the recommendation for the innovator product, Effexor XR.

Randomized, single-dose, four-period, crossover studies under fasting and nonfasting conditions comparing equal doses of the test and reference products were conducted at 37.5 mg and at 75 mg. Treatments were administered according to a randomization schedule utilizing a four treatment, four-sequence design. A single dose of venlafaxine was administered in each study period. The test formulation was Venlafaxine ER Tablets (Osmotica) and the reference formulation was Effexor XR (Venlafaxine HCl) Extended-Release Capsules (Wyeth). The test product was administered after either after an overnight fast of at least 10 hours or following a standardized high-fat breakfast which was preceded by an overnight fast of at least 10 hours. The following tables contain only the results of the effect of food after administration of venlafaxine Extended-release tablet (test) under fasting and fed conditions.

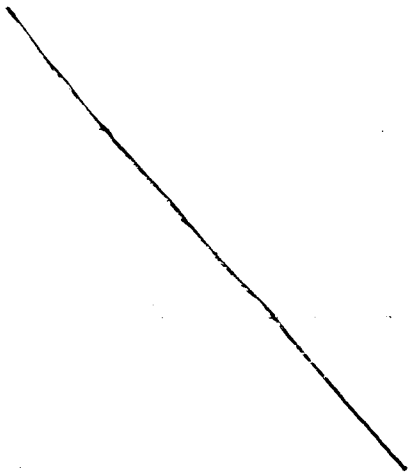
Table 13: Comparison of Venlafaxine HCl 75 mg Fed (Treatment B) vs Venlafaxine HCl 75 mg Fasted (Treatment A)

PK Parameter	Treatment B (N=31)	Treatment A (N=31)	Ratio (B/A)	90% Confidence Interval
ln AUC(0-inf)	702.90	705.20	0.9967	93.91, 105.79
ln AUC(0-t)	637.75	649.48	0.9819	92.81, 103.89
ln Cmax	42.4712	43.5372	0.9755	92.44, 102.95

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax. The units for AUCs are ng*hr/mL and Cmax are ng/mL.

Table 14: Comparison of Venlafaxine HCl 37.5 mg Fed (Treatment B) vs. Venlafaxine HCl 37.5 mg Fasted (Treatment A)

Table 16: F2 Values for Comparison of Dissolution Profile



b(4)

2.4. Analytical Methods

2.4.1. What bioanalytical methods are used to assess concentrations?

The concentrations of Venlafaxine and its metabolite O-desmethylvenlafaxine in human plasma were determined using HPLC with Fluorescence detection in two bioequivalence studies (10672001 and 10572001). The method is validated with a minimum quantifiable level of 2 ng/mL for both venlafaxine and O-desmethyl venlafaxine. The method was linear over a concentration range of 2 to 200 ng/mL. The limit of quantitation pool had an intra-assay coefficient of variation of 7.69% and 8.51% difference from theoretical. The remaining control

Specification: Q at

4 hours
12 hours
20 hours *NLT* —

b(4)

Table 15: Dissolution Test Parameter

Test	Product	Lot Number	Strength (mg)	Apparatus	Agitation Speed (rpm)	Media
1	Venlafaxine ER Tablets	P534801	37.5	II	50	pH 1.2 buffer
2	Venlafaxine ER Tablets	P534801	37.5	II	50	pH 4.5 buffer
3	Venlafaxine ER Tablets	P534801	37.5	II	50	pH 6.8 buffer
4	Venlafaxine ER Tablets	P534801	37.5	II	50	water
5	Venlafaxine ER Tablets	P534902	75	II	50	pH 1.2 buffer
6	Venlafaxine ER Tablets	P534902	75	II	50	pH 4.5 buffer
7	Venlafaxine ER Tablets	P534902	75	II	50	pH 6.8 buffer
8	Venlafaxine ER Tablets	P534902	75	II	50	water
9	Venlafaxine ER Tablets	P535002	150	II	50	pH 1.2 buffer
10	Venlafaxine ER Tablets	P535002	150	II	50	pH 4.5 buffer
11	Venlafaxine ER Tablets	P535002	150	II	50	pH 6.8 buffer
12	Venlafaxine ER Tablets	P535002	150	II	50	water
13	Venlafaxine ER Tablets	P535102	225	II	50	pH 1.2 buffer
14	Venlafaxine ER Tablets	P535102	225	II	50	pH 4.5 buffer
15	Venlafaxine ER Tablets	P535102	225	II	50	pH 6.8 buffer
16	Venlafaxine ER Tablets	P535102	225	II	50	water
17	Venlafaxine ER Tablets	P534801	37.5	II	75	water
18	Venlafaxine ER Tablets	P535102	225	II	75	water
19	Venlafaxine ER Tablets	P534801	37.5	II	100	water
20	Venlafaxine ER Tablets	P535102	225	II	100	water
21	Effexor XR	B28534	37.5	II	50	water
22	Effexor XR	B12662	75	II	50	water
23	Effexor XR	B44162	150	II	50	water
24	Effexor XR	B12662 + B44162	75 +150	II	50	water

The lots used in the dissolution testing are the same as those used in the bioequivalence studies. F2 values are provided in Table 16 below. All f2 values are greater than 50, indicating similarity of dissolution profiles for any given pair of comparison.

PK Parameter	Treatment B (N=35)	Treatment A (N=36)	Ratio (B/A)	90% Confidence Interval
ln AUC(0-inf)	449.12	431.73	1.0403	98.02, 110.40
ln AUC(0-t)	370.04	365.59	1.0122	94.86, 108.00
ln Cmax	24.4170	24.7648	0.9860	92.98, 104.55

Results are back transformed from results of ANOVA models using natural logarithms for AUC(0-inf), AUC(0-t) and Cmax. The units for AUCs are ng*hr/mL and Cmax are ng/mL.

2.3.3. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The in vitro in vivo correlation (IVIVC) model developed by the sponsor for Venlafaxine Extended Release Tablets is not acceptable at this time and cannot be used as the basis for setting the dissolution specifications. In a correspondence with the sponsor, they indicated that they prefer to use the dissolution data presented in the application to set dissolution specification and not try to justify wider specifications using IVIVC at this time. The dissolution specification is based on the dissolution of the lots used in the bioequivalence studies.

2.3.3.1. Is the proposed dissolution method and specification acceptable?

Dissolution profiles were performed to determine if varying parameters would affect the drug release rate of venlafaxine hydrochloride. The parameters varied included pH 1.2, 4.5, 6.8, and water, paddle speed (50, 75, 100 rpm), and parameters for comparing the test and reference products using Apparatus II. The following method and specification were proposed by the sponsor.

Apparatus: USP Apparatus II
Speed: 50 rpm
Meida: Water
Volume: 900 mL water

Specification:

Q at:

4 hours:
12 hours:
20 hours: NLT

b(4)

The dissolution method proposed by the sponsor is acceptable, but the specification is unacceptable. The following dissolution specification is recommended by the reviewer.

pools had intra-assay coefficients of variation ranging from 1.17% to 3.87% and percent differences within 5.54% of theoretical. The limit of quantitation pool had an inter-assay coefficient of variation of 13.7% and a -3.67% difference from theoretical. The mean recovery was 103% for QC1 with a coefficient of variation of 3.45% and 104% for QC3 with coefficient of variation of 1.18%.

For O-desmethylvenlafaxine, the limit of quantitation pool had an intra-assay coefficient of variation of 10.5% and a 2.02% difference from theoretical. The remaining quality control pools had intra-assay coefficients of variation ranging from 0.886% to 7.13% and percent differences within 8.85% of theoretical. The limit of quantitation pool had an inter-assay coefficient of variation of 13.7% and a -15.5% difference from theoretical.

The concentration of venlafaxine and O-desmethylvenlafaxine in human plasma in one of the pivotal bioequivalence study (R04-0776) was determined using High Performance Liquid Chromatography with Tandem Mass Spectrometry (LC/MS/MS). The linear range was 3 to 500 ng/mL. The calibration standards show inter-batch accuracy ranging from 99.25% to 100.66% with the CV ranging from 2.24% to 6.88%.

The analytical methods were adequately validated and acceptable.

3. Detailed Labeling Recommendations

Detailed OCP Labeling Recommendations are incorporated in the Proposed Label attached under Appendices

4. Appendix

4.1. Proposed Label with OCP recommendations
4.2. Clinical Pharmacology and Biopharmaceutics Individual Reports
4.3. DSI Report

APPEARS THIS WAY ON ORIGINAL

45 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_X_ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 3

4.2. Clinical Pharmacology and Biopharmaceutics Individual Reports

4.2.1. Title — R04-0776): A Relative Bioavailability Study of 225 mg Venlafaxine Hydrochloride Extended Release Tablets and 225 mg (150 mg and 75 mg Effexor® XR) Capsules Under Fed Conditions

b(4)

Objectives: To compare the relative bioavailability (rate and extent of absorption) of Venlafaxine Hydrochloride Extended Release (ER) Tablets 225 mg by Osmotica Pharmaceutical Corp. with that of Effexor XR® Capsules 225 mg (150 mg and 75 mg) by Wyeth Pharmaceuticals, Inc. following a single, oral dose (1 x 225 mg extended-release tablet or 1 x 150 mg plus 1 x 75 mg extended-release capsule) in healthy, adult subjects under non-fasting conditions.

Study Design: This was a single-center, randomized, two-way crossover study conducted under nonfasting conditions. Thirty-six (36) subjects were enrolled in the study. The mean age and weight were 33.1 ± 12.9 years and 160.6 ± 29.6 lbs, respectively. On study day 1, each subject received either a single, oral dose (1 x 225 mg extended release tablet) of the test product, Venlafaxine ER Tablets 225 mg, or a single, combined oral dose of the reference product, Effexor XR® Extended-Release Capsules 150 mg and 75 mg. Drug administration was assisted with 240 mL of ambient temperature water. Dosing occurred 30minutes after the initiation of a standardized, high fat breakfast (2 eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, 4 ounces of hash brown potatoes and 8 ounces of whole milk) preceded by an overnight fast. Following a seven day washout period, subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization. Plasma concentration data from 28 of 36 subjects were used in the statistical analysis. During each study period, 20 blood samples (7 mL each) were collected from each subject within one hour prior to dosing (0 hour) and after dose administration at study hours 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 36, 48, and 72 hours. The test product was Venlafaxine ER Tablets 225 mg, Lot no. P535102. The reference product were Effexor XR Capsules 150 mg, Lot no. B44162 and Effexor XR 75 mg capsules, lot no. B12662.

Analytical Method: An LC/MS/MS method was used to determine the concentration of Venlafaxine and its major metabolite (D, L-O-Desmethylvenlafaxine) in human plasma. The concentration range was 3 to 500 ng/mL. The accuracy was between 94% to 108.8% and the precision was 0.83% to 2.95%.

Data Analysis: Pharmacokinetic parameters were computed by using non-compartmental methods.

Results: The following tables summarize the results of the analyses performed on the pharmacokinetic parameters. The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80% and 125% limits for the pharmacokinetic parameters Cmax, AUC0-t, and AUC0-inf of the ln-transformed

data. The results of this study indicate bioequivalence between the test and reference products under fed conditions.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Venlafaxine N=28				
Parameter	**Test**	**Reference**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	2343.99	2137.48	109.66	(103.8, 115.85)
AUC_{0-inf} (ng-hr/mL)	2431.98	2254.30	107.88	(102.64, 113.39)
C_{max} (ng/mL)	132.34	130.42	101.47	(94.15, 109.37)

Safety Evaluation: The sponsor reported that in general, the clinical portion of the project was completed without any significant sequelae attributable to the investigational drug. The clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study exit were considered directly attributable to the product.

The sponsor reported that Adverse events (AE) were mild to moderate in severity. The most frequently occurring AE that occurred following the oral administration of the test product, Venlafaxine ER Tablets 225 mg, was nausea. The most frequently occurring AE following the oral administration of the reference product, Effexor XR® Extended-Release Capsules 150 mg and Effexor® XR Extended-Release Capsules 75 mg, was dizziness. There were 70 adverse events considered related to the oral administration of Venlafaxine ER Tablets 225 mg. There were 64 adverse events considered related to the oral administration of Effexor XR Extended-Release Capsules 150 mg and Effexor® XR Extended-Release Capsules 75 mg.

Overall venlafaxine was reported to be well tolerated as a single, oral dose (1 x 225 mg extended release tablet or 1 x 150 mg plus 1 x 75 mg extended-release capsules) of 225 mg administered under non-fasting conditions.

Overall Conclusion: The results of the study indicated bioequivalence between the test and reference products under fed conditions.

Reviewer Comments: The reviewer agrees with the sponsor's conclusions. Venlafaxine 225 mg extended release tablets are bioequivalent to 225 mg Effexor XR (1 x 150 mg plus 75 mg extended release capsules) under fed conditions.

Attachments

Table 14.2 Summary of Statistical Analysis

Venlafaxine
N=28

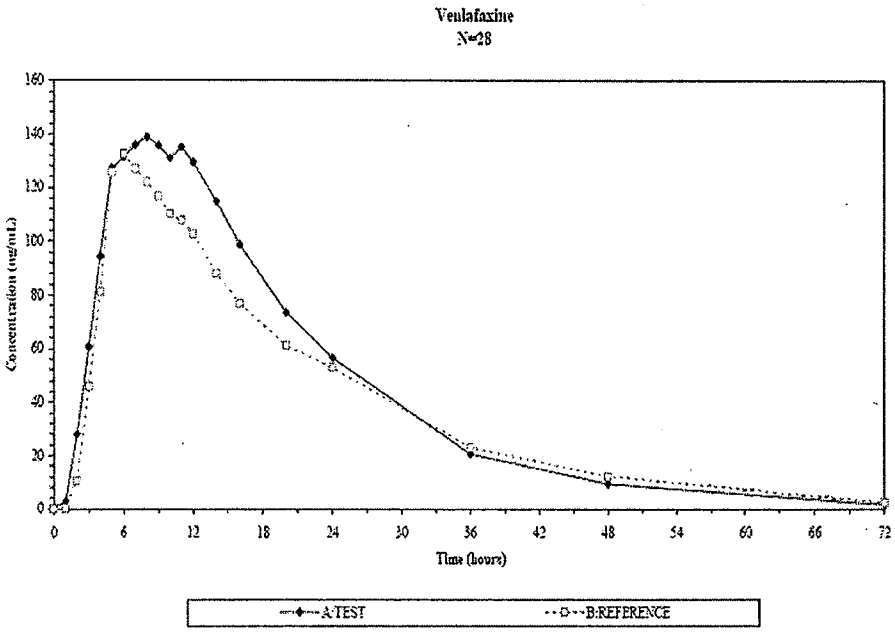
Ln-Transformed Data

PK Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test	Reference	Test	Reference	% Ratio	(Lower Limit, Upper Limit)			
C_{max}	4.885	4.871	132.54	130.42	101.47	(94.15, 109.37)	0.7416	0.9983	16.37%
AUC_{0-t}	7.760	7.667	2343.99	2137.48	109.66	(103.8, 115.85)	0.0082	1.0000	11.97%
AUC_{0-inf}	7.796	7.721	2431.98	2254.30	107.88	(102.64, 113.39)	0.0153	1.0000	10.85%

PK Variable	Least Squares Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA
	Test	Reference	% Ratio	(Lower Limit, Upper Limit)		
C_{max}	154.04	147.10	104.72	(97.45, 111.99)	0.2786	0.9946
AUC_{0-t}	3052.35	2721.88	112.14	(105.44, 118.84)	0.0047	0.9983
AUC_{0-inf}	3138.09	2850.04	110.11	(103.93, 116.28)	0.0097	0.9996
T_{max}	8.19	6.39	128.22	(115.51, 140.94)	0.0068	0.7332
k_e	0.0908	0.0696	130.51	(122.03, 139)	<0.0001	0.9718
$t_{1/2}$	8.31	10.83	76.68	(68.54, 84.81)	<0.0001	0.9809

Geometric means are based on least squares means of ln-transformed values.

Mean Plasma Concentration (0- 72 hrs)



OSMOTICA PHARMACEUTICAL CORP
VENLAFAXINE 225 MG ER TABLETS
—— , STUDY NO. R04-0776
FED
Venlafaxine
DESCRIPTIVE STATISTICS FOR PHARMACOKINETIC DATA BY PRODUCT

b(4)

PRODUCT=A:TEST

The MEANS Procedure

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
AUCT	28	2967.418	2513.258	84.695		
AUCINF	28	3052.698	2559.762	83.852		
CMAX	28	151.322	92.405	61.085		
TMAX	28	8.143	2.121	26.044		
KE	28	0.091	0.025	27.746		
THALF	28	8.265	2.602	31.484		
LAUCT	28	7.739	0.708	9.143		
LAUCINF	28	7.776	0.690	8.871		
LCMAX	28	4.870	0.550	11.297		

b(4)

PRODUCT=B:REF

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
AUCT	28	2669.590	2145.039	80.351		
AUCINF	28	2795.279	2208.052	78.992		
CMAX	28	147.089	78.012	53.037		
TMAX	28	6.321	1.827	28.899		
KE	28	0.089	0.022	31.198		
THALF	28	10.806	2.958	27.375		
LAUCT	28	7.657	0.668	8.729		
LAUCINF	28	7.710	0.659	8.549		
LCMAX	28	4.874	0.485	9.948		

b(4)

Summary of Statistical Analysis
Desmethylvenlafaxine
N=28

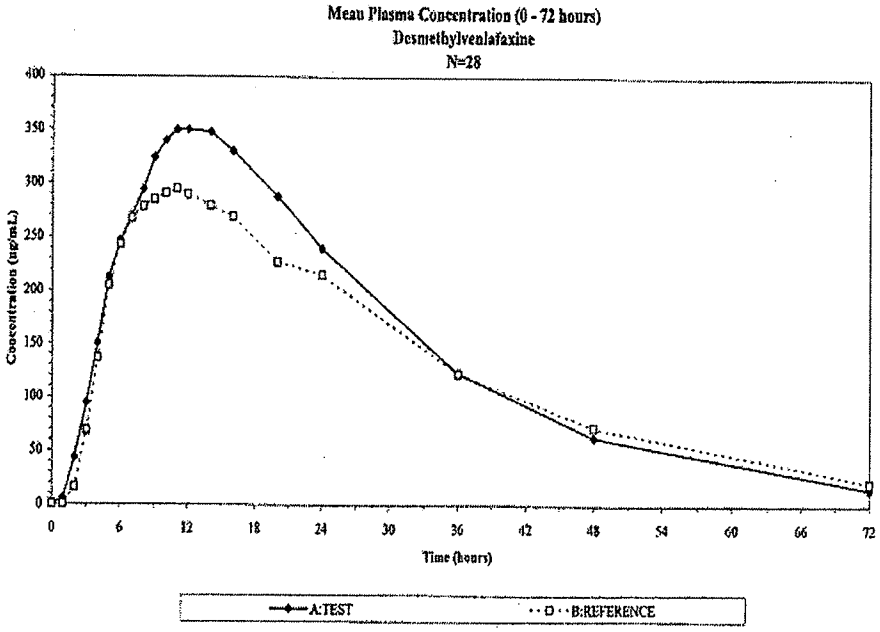
Ln-Transformed Data

PK Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test	Reference	Test	Reference	% Ratio	(Lower Limit, Upper Limit)			
C_{max}	5.835	5.667	341.95	289.28	118.21	(112.49, 124.21)	<0.0001	1.0000	10.79%
AUC_{0-t}	9.201	9.105	9910.07	9004.41	110.06	(106.35, 113.89)	<0.0001	1.0000	7.45%
$AUC_{0-\infty}$	9.231	9.160	10204.96	9507.14	107.34	(103.83, 110.97)	0.0012	1.0000	7.23%

Non-Transformed Data

PK Variable	Least Squares Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA
	Test	Reference	% Ratio	(Lower Limit, Upper Limit)		
C_{max}	366.03	309.66	118.20	(112.94, 123.46)	<0.0001	1.0000
AUC_{0-t}	10347.83	9459.29	109.39	(106.03, 112.76)	<0.0001	1.0000
$AUC_{0-\infty}$	10638.73	9980.32	106.60	(103.3, 109.89)	0.0021	1.0000
T_{max}	12.56	11.63	108.05	(97.66, 118.44)	0.1981	0.8849
k_e	0.0590	0.0513	115.12	(108.81, 121.43)	0.0004	0.9994
$t_{1/2}$	12.08	14.32	84.37	(79.04, 89.69)	<0.0001	1.0000

Geometric means are based on least squares means of ln-transformed values.



Desmethylvenlafaxine

b(4)

VENLAFAXINE 225 MG ER TABLETS
— STUDY NO. R04-0776
FED
DESCRIPTIVE STATISTICS FOR PHARMACOKINETIC DATA BY PRODUCT

PRODUCT=A:TEST

The MEANS Procedure

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
AUCT	28	10449.707	2995.649	28.667		
AUCINF	28	10738.959	3048.011	28.383		
CMAX	28	370.322	126.684	34.209		
TMAX	28	12.500	2.548	20.367		
KE	28	0.059	0.010	17.296		
THALF	28	12.011	1.957	16.291		
LAUCT	28	9.214	0.293	3.178		
LAUCINF	28	9.243	0.286	3.096		
LCMAX	28	5.850	0.381	6.513		

b(4)

PRODUCT=B:REF

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum
AUCT	28	9565.229	3020.177	31.575		
AUCINF	28	10094.272	3187.279	31.575		
CMAX	28	313.411	106.515	33.986		
TMAX	28	11.430	4.167	36.459		
KE	28	0.051	0.014	27.159		
THALF	28	14.309	3.080	21.529		
LAUCT	28	9.118	0.315	3.451		
LAUCINF	28	9.173	0.311	3.394		
LCMAX	28	5.685	0.377	6.628		

b(4)

4.2.2. Title (Protocol 10572001): A Study to Evaluate the Bioequivalence of Venlafaxine HCl 75mg Extended Release Tablets (Osmotica) Compared to Effexor® XR 75mg Extended Release Capsules (Wyeth) Under Fasted and Fed Conditions in Healthy Adult Subjects.

Objective: To evaluate the bioequivalence of Venlafaxine HCl 75 mg extended release tablets (Osmotica) to Effexor XR (Venlafaxine hydrochloride) 75 mg extended release capsules (Wyeth) under fasted and fed conditions in healthy adult subjects

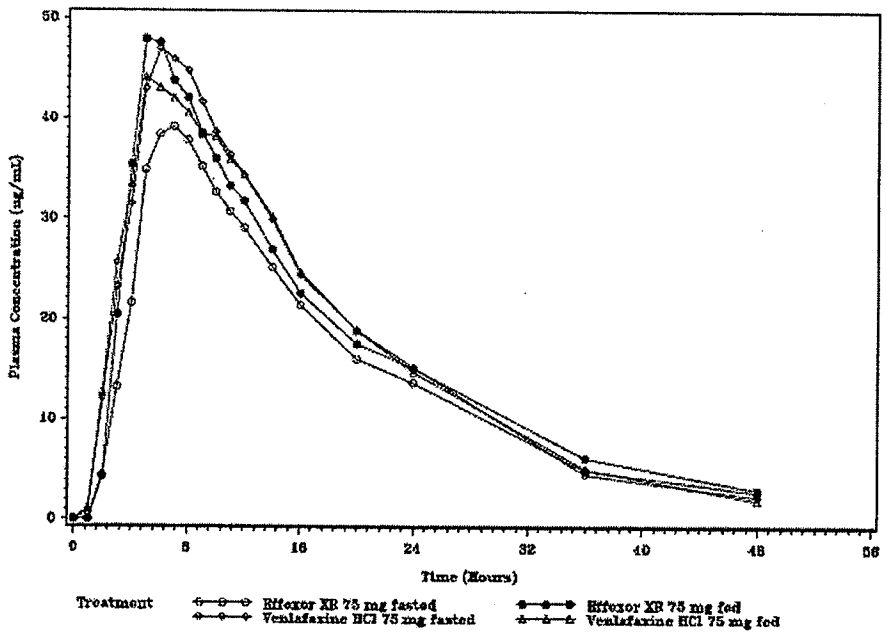
Study Design: This was a randomized, single-dose, four-period, crossover study under fasting and nonfasting conditions comparing equal doses of the test and reference products. The study population included 36 healthy adult subjects who satisfied all entry criteria. The 30 subjects (22 males and 8 females) who participated in and completed this study were healthy, in the age range of 18 to 48 (mean age 33.5) years, with a weight in the range of 131 to 216 (mean weight 172.7) lbs and a Body Mass Index (BMI) between 20.8 and 29.9 (mean BMI 25.6) kg/m2. The subject population consisted of 19 Black, 9 Hispanic, and 2 Caucasian subjects. Treatments were administered according to a randomization schedule utilizing a four treatment, four-sequence design. Subjects were randomized to one of the following four sequences: ABCD, BCDA, CDAB, DABC. A single dose of 75 mg venlafaxine was administered in each study period. The test formulation was Venlafaxine ER Tablets 75 mg (Osmotica Pharmaceutical Corporation, Lot no. P534902), and the reference formulation was Effexor_XR (Venlafaxine HCl) Extended-Release Capsules (Wyeth Pharmaceuticals, Inc., Lot no. B12662). The subjects received the test product in two study periods and the reference product in the other two study periods. The test/reference products were administered after an overnight fast of at least 10 hours (Test A or Reference C) and following a standardized high-fat breakfast preceded by an overnight fast of at least 10 hours (Test B or Reference D). The order of administration was according to the dosing randomization schedule. There was a 7-day interval between treatments. Blood samples were collected pre-dose (0) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 36, 48, and 60 hours post-dose. Subjects were confined at the clinical facility from at least 12 hours prior to dosing until after the 24-hour blood collection.

Analytical Method: Samples for determination of venlafaxine and O-desmethylvenlafaxine were analyzed with HPLC with fluorescence detection. The minimum quantifiable level was 2.0 ng/mL for both venlafaxine and O-desmethylvenlafaxine. The validated assay has an analytical range of 2 – 200 ng/mL. The quality control pools for venlafaxine had intra-assay coefficient 1.17% to 3.87%. The mean recovery for venlafaxine was 103%. The interassay coefficient of variation was 2.68 to 3.36%. The quality control pools for O-desmethylvenlafaxine had an intra-assay coefficient of variation ranging from 0.886% to 7.13%. The interassay coefficient of variation was 1.91 % to 9.02%. The mean recovery of O-desmethylvenlafaxine was 92.4%.

Data Analysis: The pharmacokinetic parameters were determined using non-compartmental methods. Confidence intervals (90%) for the comparison of test and reference area and peak results were constructed to test two, one-sided hypotheses at the $\alpha = 0.05$ level of significance. The confidence intervals were presented for the ratio of the test-to-reference treatment means, and for the ratio of the geometric means (obtained from logarithmic transformation). ANOVA was performed using the Proc Mixed statistical procedure with period, sequence and treatment as fixed effects and subject nested within sequence as a random effect. On condition that the 90% confidence intervals of log-transformed Cmax, AUC(0-t), and AUC(0-inf) fell within the range 0.80 to 1.25 for venlafaxine when comparing Test A with Reference C and Test B with Reference D, then bioequivalence was deemed to have been demonstrated in both the fasted and fed states. Additional analyses to compare the effect of food on the pharmacokinetics of both the reference product (Reference B versus Reference D) and the test product (Test A versus Test B) were also generated.

Results: The mean plasma concentration time profile for venlafaxine is provided in the following figure.

Mean Venlafaxine Plasma Concentrations versus Time



The following tables contain the pharmacokinetic parameters and the results of the statistical analysis for venlafaxine and O-desmethylvenlafaxine.

Comparison of Venlafaxine HCl 75 mg Fasted (Treatment A) vs Effexor XR 75 mg Fasted (Treatment C)

PK Parameter	Treatment A (N=31)	Treatment C (N=30)	Ratio (A/C)	90% Confidence Interval
ln AUC(0-inf)	705.20	620.90	1.1358	106.86, 120.71
ln AUC(0-t)	649.48	552.04	1.1765	111.11, 124.57
ln Cmax	43.5372	36.4611	1.1941	113.07, 126.10

Comparison of Venlafaxine HCl 75 mg Fed (Treatment B) vs Effexor XR 75 mg Fed (Treatment D)

PK Parameter	Treatment B (N=31)	Treatment D (N=31)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	702.90	696.28	1.0095	95.05, 107.21
ln AUC(0-t)	637.75	622.28	1.0249	96.80, 108.50
ln Cmax	42.4712	44.4441	0.9556	90.50, 100.90

Statistical comparisons of ln-transformed AUC(0-inf) and AUC(0-t), for the test treatment vs. reference treatment under fasted conditions, resulted in 90% confidence intervals (CI) for the ratios of least square means (LSM) within the stipulated range of 80-125%. However, the 90% CI for Cmax was above the stipulated range of 80-125% with an interval of (113.1, 126.1).

Statistical comparisons of the test vs. reference treatments under fed conditions resulted in the 90% CI for AUC(0-inf), AUC(0-t) and Cmax of venlafaxine falling within the recommended range of 80-125%.

Comparison of Venlafaxine HCl 75 mg Fed (Treatment B) vs Venlafaxine HCl 75 mg Fasted (Treatment A)

PK Parameter	Treatment B (N=31)	Treatment A (N=31)	Ratio (B/A)	90% Confidence Interval
ln AUC(0-inf)	702.90	705.20	0.9967	93.91, 105.79
ln AUC(0-t)	637.75	649.48	0.9819	92.81, 103.89
ln Cmax	42.4712	43.5372	0.9755	92.44, 102.95

Comparison of Effexor XR 75 mg Fed (Treatment D) vs Effexor XR 75 mg Fasted (Treatment C)

PK Parameter	Treatment D (N=31)	Treatment C (N=30)	Ratio (D/C)	90% Confidence Interval
ln AUC(0-inf)	696.28	620.90	1.1214	105.51, 119.19
ln AUC(0-t)	622.28	552.04	1.1272	106.46, 119.35
ln Cmax	44.4441	36.4611	1.2189	115.43, 128.72

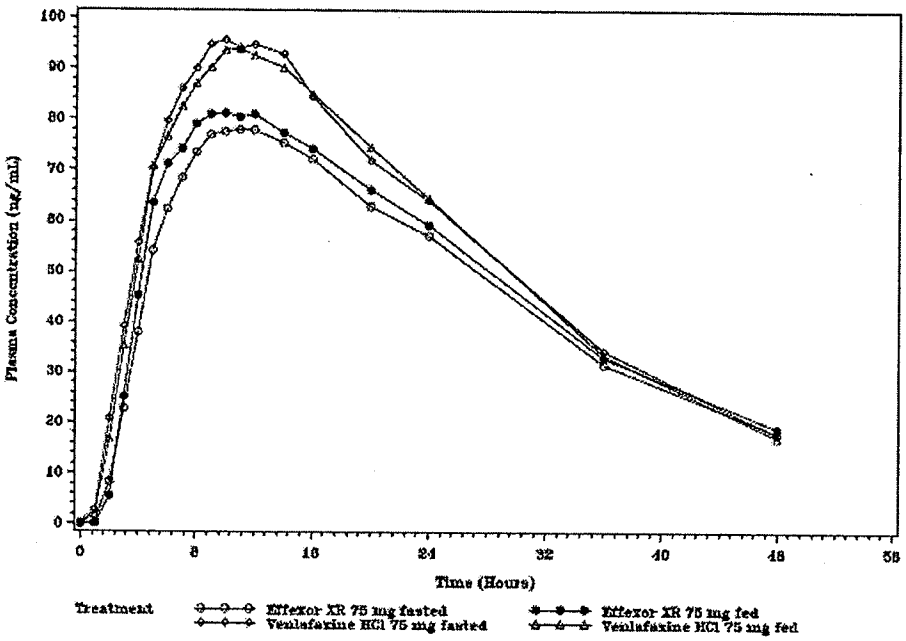
Statistical comparison of Venlafaxine Extended Release tablets (Osmotica) treatment in fed vs fasted conditions resulted in 90% CI for the ratios of least square mean (LSM) for AUC(0-inf), AUC(0-t) and Cmax falling within the stipulated range of 80-125%.

Statistical comparison of reference (Effexor XR) treatment in fed vs fasted conditions resulted in 90% CI for the ratios of least square mean (LSM) for AUC(0-inf) and AUC(0-t) falling within the stipulated range of 80-125%. However, the 90%CI for Cmax exceeded the stipulated range of 80-125% (115.4, 128.7).

O-desmethylvenlafaxine (ODV)

The mean ODV concentrations over time by treatment is contained in the following figure.

Mean ODV Plasma Concentrations versus Time



The mean pharmacokinetic parameters for ODV and the 90% confidence interval are provided in the following tables.

Comparison of O-desmethylvenlafaxine after administration of Venlafaxine HCl 75 mg fasted (Treatment A) vs Effexor XR 75 mg Fasted (Treatment C)

PK Parameter	Treatment A (N=31)	Treatment C (N=30)	Ratio (A/C)	90% Confidence Interval
ln AUC(0-inf)	2890.81	2538.45	1.1388	109.83, 118.08
ln AUC(0-t)	2670.33	2290.82	1.1657	112.73, 120.53
ln Cmax	95.1662	78.5067	1.2122	117.33, 125.25

Comparison of O-desmethylvenlafaxine after administration of Venlafaxine HCl 75 mg Fed (Treatment B) vs Effexor XR 75 mg Fed (Treatment D)

PK Parameter	Treatment B (N=31)	Treatment D (N=31)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	2823.87	2709.14	1.0424	100.54, 108.06
ln AUC(0-t)	2614.65	2450.05	1.0672	103.22, 110.34
ln Cmax	92.1043	84.2117	1.0937	105.87, 113.00

Comparison of O-desmethylvenlafaxine after administration of Venlafaxine HCl 75 mg Fed (Treatment B) vs Venlafaxine HCl 75 mg Fasted (Treatment A)

PK Parameter	Treatment B (N=31)	Treatment A (N=31)	Ratio (B/A)	90% Confidence Interval
ln AUC(0-inf)	2823.87	2890.81	0.9768	94.27, 101.22
ln AUC(0-t)	2614.65	2670.33	0.9792	94.74, 101.20
ln Cmax	92.1043	95.1662	0.9678	93.71, 99.95

Comparison of O-desvenlafaxine after administration of Effexor XR 75 mg fed (Treatment D) vs Effexor XR 75 mg Fasted (Treatment C)

PK Parameter	Treatment D (N=31)	Treatment C (N=30)	Ratio (D/C)	90% Confidence Interval
ln AUC(0-inf)	2709.14	2538.45	1.0672	102.89, 110.70
ln AUC(0-t)	2450.05	2290.82	1.0695	103.44, 110.59
ln Cmax	84.2117	78.5067	1.0727	103.82, 110.83

Statistical comparisons of the test treatment in fed vs. fasted conditions resulted in the 90% CI for AUC(0-inf) and AUC(0-t) of ODV falling within the recommended range of 80-125%. However, the 90% CI for Cmax was above the stipulated range of 80-125% (117.3 – 125.5); this is not expected to be clinically significant.

Pharmacokinetic Summary: Under fasting conditions the 90% CI for Venlafaxine ER formulation (Osmotica) compared to Effexor XR® (Wyeth) with respect to AUC(0-inf) and AUC(0-t) for the parent compound Venlafaxine were (106.9, 120.7) and (111.1, 124.6), respectively. However, the Venlafaxine ER formulation to Effexor XR had a 90% CI values of (113.1, 126.1).

The Venlafaxine ER formulation was bioequivalent to Effexor XR® with respect to the primary log transformed PK parameters (AUC(0-inf), AUC(0-t) and Cmax) for the parent compound Venlafaxine with 90% CI of (95.1, 107.2), (96.8, 108.5) and (90.5, 100.9), respectively in the fed state.

In addition, Venlafaxine ER is equivalent to Effexor XR® with respect to AUC parameters for O-desmethylvenlafaxine metabolite in both the fasted and fed states; Cmax values of ODV in the fasted state were greater than the stipulated range of 80-125% (117.33 – 125.5).

No significant difference was observed for the test treatment, when comparing fed vs. fasted conditions for venlafaxine and ODV. No significant difference on total exposure was observed for the reference treatment when comparing fed vs. fasted states. However, the Cmax for venlafaxine was greater for fed vs. fasted (115.4, 128.7), for the reference (Effexor XR) treatment.

Safety Summary: The sponsor reported that the most frequently reported adverse event occurring after receipt of Venlafaxine 75 mg Extended Release under Fasted and Fed conditions and Effexor XR under Fasted conditions was nausea. The most frequently reported adverse event occurring after receipt of Reference D was somnolence.

The most frequently reported adverse event occurring after receipt of Effexor XR in the Fed state was somnolence. The sponsor reported that all adverse events were mild or moderate. No serious adverse events occurred during the study.

Reviewer's conclusions: Venlafaxine Extended Release 75 mg is not bioequivalent to Effexor XR mg under fasting conditions. Exposure in terms of AUC after administration of Venlafaxine Extended Release was equivalent to Effexor XR 75 mg. But Cmax was about 19% higher under fasting conditions and the 90% confidence interval was not contained within the recommended 80% to 125% limit.

Venlafaxine Extended Release 75 mg Tablet is bioequivalent to Effexor XR 75 mg capsules under fed conditions. The 90% CI for AUC and Cmax were contained within the 80% to 12% regulatory criteria. Food does not appear to significantly affect the absorption of Venlafaxine Extended Release Tablets.

Attachment

Summary of Pharmacokinetic Parameters of Venlafaxine for Each Treatment

Venlafaxine Hydrochloride Pharmacokinetic Data
Arithmetic Means (CV%) in 33 Subjects

PK Parameter	N	Venlafaxine HCl 75 mg fasted (A)	N	Venlafaxine HCl 75 mg fed (B)	N	Effexor XR 75 mg fasted (C)
AUC(0-inf) (ng.hr/mL)	31	890.12(75.85%)	31	861.76(72.02%)	29	770.93(68.25%)
AUC(0-t) (ng.hr/mL)	31	827.24(74.84%)	31	798.46(74.23%)	30	709.08(67.15%)
Cmax (ng/mL)	31	48.60(47.14%)	31	46.62(43.10%)	30	40.85(41.84%)
T 1/2 (hr)	31	8.58(46.35%)	31	8.66(32.11%)	29	11.72(49.42%)
Kel (1/hr)	31	0.0915(30.29%)	31	0.0878(31.75%)	29	0.0692(34.48%)
Tmax (hr)	31	6.61(16.85%)	31	6.26(31.13%)	30	6.77(17.65%)

PK Parameter	N	Effexor XR 75 mg fed (D)	A/C	B/D	B/A	D/C
AUC(0-inf) (ng.hr/mL)	31	877.92(77.22%)	1.1546061	0.9815971	0.9681396	1.1387766
AUC(0-t) (ng.hr/mL)	31	802.24(77.12%)	1.1816232	0.9952788	0.9652117	1.1459266
Cmax (ng/mL)	31	50.29(46.86%)	1.1869888	0.9269403	0.9591159	1.2281909
T 1/2 (hr)	31	10.73(30.06%)	0.7315527	0.8073133	1.0101359	0.9153544
Kel (1/hr)	31	0.0688(22.85%)	1.3211921	1.2765259	0.9599425	0.9935313
Tmax (hr)	31	5.71(23.58%)	0.9774194	1.0961582	0.9463005	0.8437947

Summary of Pharmacokinetic Parameters of O-desmethylvenlafaxine for Each Treatment

O-desmethyl Venlafaxine Pharmacokinetic Data
Arithmetic Means (CV%) in 33 Subjects

PK Parameter	N	Venlafaxine HCl 75 mg fasted (A)	N	Venlafaxine HCl 75 mg fed (B)	N	Effexor XR 75 mg fasted (C)
AUC(0-inf) (ng.hr/mL)	31	2972.97(24.79%)	31	2928.88(25.51%)	29	2647.67(29.85%)
AUC(0-t) (ng.hr/mL)	31	2781.68(24.64%)	31	2751.07(26.07%)	30	2590.54(28.97%)
Cmax (ng/mL)	31	100.73(31.01%)	31	97.93(30.06%)	30	81.50(29.29%)
T 1/2 (hr)	31	12.68(31.10%)	31	12.52(23.73%)	29	14.10(27.39%)
Kel (1/hr)	31	0.0590(26.85%)	31	0.0584(23.41%)	29	0.0527(28.82%)
Tmax (hr)	31	11.55(26.24%)	31	11.58(24.80%)	30	12.07(25.65%)

PK Parameter	N	Effexor XR 75 mg fed (D)	A/C	B/D	B/A	D/C
AUC(0-inf) (ng.hr/mL)	31	2799.80(27.62%)	1.1227764	1.0453128	0.9844233	1.0573745
AUC(0-t) (ng.hr/mL)	31	2515.13(26.62%)	1.163622	1.0938113	0.9889957	1.0521187
Cmax (ng/mL)	31	87.30(30.25%)	1.2360292	1.1218314	0.9722035	1.0711699
T 1/2 (hr)	31	14.68(26.82%)	0.8993953	0.8527096	0.987294	1.0413481
Kel (1/hr)	31	0.0509(29.33%)	1.1194727	1.1472439	0.9886356	0.9647037
Tmax (hr)	31	10.29(35.32%)	0.9571289	1.1253918	1.0027093	0.8527892

4.2.3. Title (Protocol No. 10672001): A Study to Evaluate the Bioequivalence of Venlafaxine HCl 37.5 mg Extended Release Tablets (Osmotica) Compared to Effexor® XR 37.5 mg Extended Release Capsules (Wyeth) Under Fasted and Fed Conditions in Healthy Adult Subjects

Objectives: To evaluate the bioequivalence of Osmotica Pharmaceutical Corporation's Venlafaxine HCl 37.5 mg extended release tablets compared to Effexor® XR (venlafaxine hydrochloride) 37.5mg extended-release capsules (Wyeth) under fasted and fed conditions in healthy adult subjects.

Study Design: This was a randomized, single-dose, four-period, crossover study under fasting and nonfasting conditions comparing equal doses of the test and reference products. Thirty six healthy adults participated in the study. In each study period, a single 37.5 mg dose was administered to all subjects following an overnight fast or following a standardized breakfast preceded by an overnight fast. The test formulation was Venlafaxine ER Tablets 37.5 mg (Osmotica Pharmaceutical Corporation), and the reference formulation was (Venlafaxine HCl) Extended-Release Capsules (Wyeth Pharmaceuticals, Inc.). The subjects received the test product in two study periods and the reference product in the other two study periods; the order of administration was according to the dosing randomization schedule. The treatments administered were Treatment A: Venlafaxine HCl 37.5 mg ER Fasted, Treatment B: Venlafaxine HCl 37.5 mg ER Fed, Treatment C: Effexor XR 37.5 mg Fasted and Treatment D: Effexor XR 37.5 mg Fed. There was a 7-day interval between treatments. Blood samples (6 mL) were drawn in sodium heparin vacutainers prior to dosing and at the following nominal times after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 36, 48, and 60 hours.

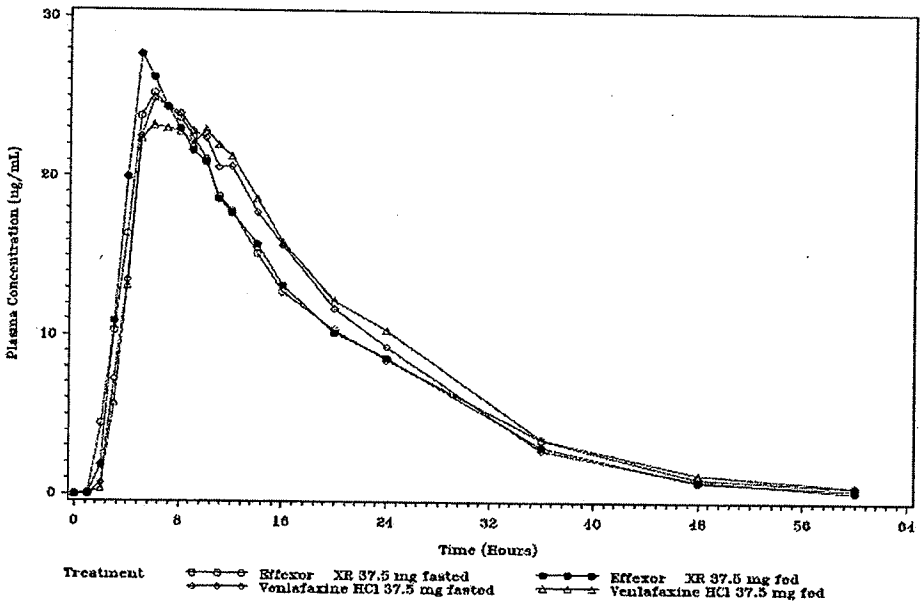
Analytical Method: HPLC with Fluorescence Detection was used for the analysis of Venlafaxine and O-Desmethyl venlafaxine. The minimum quantifiable level was 2 ng/mL. The validated assay had analytical range of 2 to 200 ng/mL. The limit of quantitation pool had an intra-assay coefficient of variation (CV) of 7.69% and a 8.51% difference from theoretical. The remaining quality control pools had intra-assay coefficients of variation ranging from 1.17% to 3.87%. For O-Desmethylvenlafaxine, the limit of quantitation pool had an intra-assay coefficient of variation of 10.5% and a 2.02% difference from theoretical. The remaining quality control pools had intra-assay coefficients of variation ranging 0.886% to 7.13% and percent differences within 8.85% of theoretical.

The limit of quantitation pool had an inter-assay coefficient of variation of 13.7% and a -3.67% difference from theoretical. The remaining quality control pools had inter-assay coefficients of variation ranging from 2.68% to 3.36% and percent differences within 3.31% of theoretical. For O-Desmethylvenlafaxine, the limit of quantitation pool had an inter-assay coefficient of variation of 13.7% and a -15.5% difference from theoretical. The remaining quality control pools had inter-assay coefficients of variation ranging from 1.91% to 9.02% and percent differences within 7.56% of theoretical.

Data Analysis: Pharmacokinetic parameters were calculated using non-compartmental means.

Results: The following figure presents the plots of the mean venlafaxine concentrations over time by treatment.

Mean Venlafaxine Plasma Concentrations versus Time



The following tables provide a summary of pharmacokinetic parameters after administration of the 4 treatments.

Summary of Pharmacokinetic Parameters of Venlafaxine for Each Treatment

Venlafaxine Pharmacokinetic Data
Arithmetic Means (CV%) in 36 Subjects

PK Parameter	N	Venlafaxine HCl 37.5 mg fasted (A)	N	Venlafaxine HCl 37.5 mg fed (B)	N	Effexor XR 37.5 mg fasted (C)
AUC(0-inf) (ng.hr/mL)	36	499.17(59.15%)	34	551.14(92.89%)	35	494.96(90.79%)
AUC(0-t) (ng.hr/mL)	36	441.79(58.29%)	35	459.95(91.99%)	35	435.81(90.83%)
Cmax (ng/mL)	36	27.42(47.93%)	35	26.90(49.98%)	35	26.27(48.36%)
T 1/2 (hr)	36	9.69(38.06%)	34	9.98(27.42%)	35	10.19(34.02%)
Kel (1/hr)	36	0.0783(26.49%)	34	0.0731(20.63%)	35	0.0752(33.11%)
Tmax (hr)	36	7.36(26.21%)	35	7.09(30.49%)	35	6.37(19.07%)

PK Parameter	N	Effexor XR 37.5 mg fed (D)	A/C	B/D	B/A	D/C
AUC(0-inf) (ng.hr/mL)	33	489.28(70.58%)	1.0085046	1.1264669	1.1041183	0.9884984
AUC(0-t) (ng.hr/mL)	35	430.27(71.25%)	1.0137389	1.068971	1.0410891	0.9872978
Cmax (ng/mL)	35	28.61(35.66%)	1.0440922	0.9403435	0.9810335	1.0892715
T 1/2 (hr)	33	9.34(23.49%)	0.9512892	1.0696564	1.030274	0.9162639
Kel (1/hr)	33	0.0779(22.90%)	1.0106653	0.938247	0.9336136	1.035546
Tmax (hr)	35	5.43(18.56%)	1.1553313	1.3052632	0.9825876	0.8520179

Treatment A: Venlafaxine HCl ER 37.5 mg Fasted, Treatment B: Venlafaxine HCl 37.5 mg ER Fed, Treatment C: Effexor XR 37.5 mg Fasted, Treatment D: Effexor XR 37.5 mg Fed.

Statistical comparisons of ln-transformed AUC(0-inf), AUC(0-t) and Cmax for the test treatment vs. reference treatment under the various treatment conditions and the resulted 90% confidence intervals (CI) for the ratios of the means are provided in the following tables. In comparing the test vs. reference treatments under fed conditions, the 90% CI fell within the stipulated range of 80-125% for AUC(0-inf), AUC(0-t) and Cmax.

Statistical comparison of test treatment under fed vs fasted conditions resulted in 90% CI within the recommended range of 80-125% for the ratios of means for AUC(0-inf), AUC(0-t) and Cmax within the recommended range of 80 – 125%. Statistical comparison of reference treatment under fed vs fasted conditions resulted in 90% CI for the ratios of means for AUC(0-inf), AUC(0-t) and Cmax within the recommended range of 80-125%.

Comparison of Venlafaxine HCl 37.5 mg Fasted (Treatment A) vs Effexor XR 37.5 mg Fasted (Treatment C)

PK Parameter	Treatment A (N=36)	Treatment C (N=35)	Ratio (A/C)	90% Confidence Interval
ln AUC(0-inf)	431.73	405.80	1.0639	100.31, 112.85
ln AUC(0-t)	365.59	351.14	1.0411	97.58, 111.09
ln Cmax	24.7648	24.4327	1.0136	95.58, 107.48

Comparison of Venlafaxine HCl 37.5 mg Fed (Treatment B) vs. Effexor XR 37.5 mg Fed (Treatment D)

PK Parameter	Treatment B (N=35)	Treatment D (N=35)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	449.12	426.73	1.0525	98.98, 111.91
ln AUC(0-t)	370.04	370.71	0.9982	93.49, 106.58
ln Cmax	24.4170	27.3110	0.8940	84.26, 94.86

Comparison of Venlafaxine HCl 37.5 mg Fed (Treatment B) vs. Venlafaxine HCl 37.5 mg Fasted (Treatment A)

PK Parameter	Treatment B (N=35)	Treatment A (N=36)	Ratio (B/A)	90% Confidence Interval
ln AUC(0-inf)	449.12	431.73	1.0403	98.02, 110.40
ln AUC(0-t)	370.04	365.59	1.0122	94.86, 108.00
ln Cmax	24.4170	24.7648	0.9860	92.98, 104.55

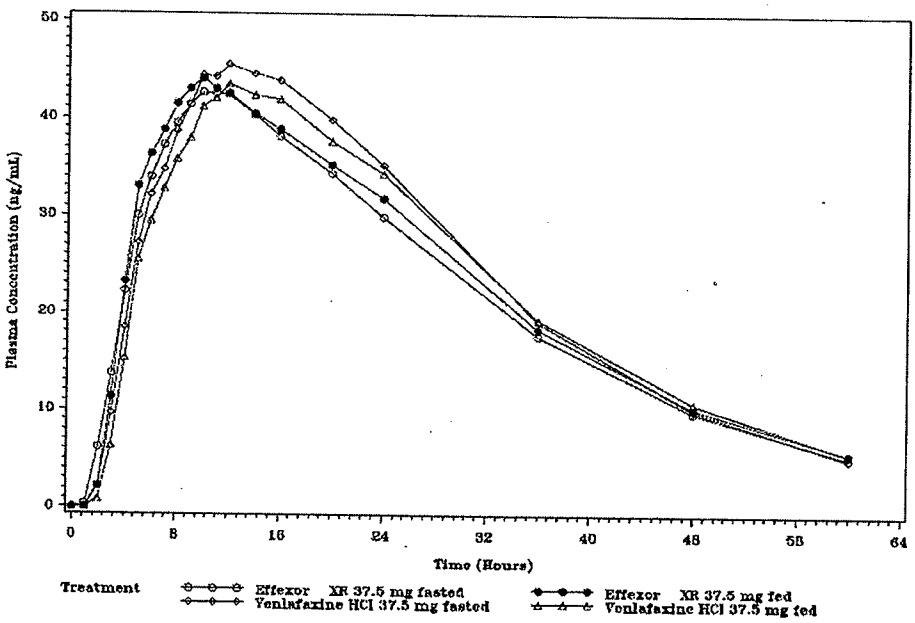
Comparison of Effexor 37.5 mg Fed (Treatment D) vs. Effexor XR 37.5 mg Fasted (Treatment C)

PK Parameter	Treatment D (N=35)	Treatment C (N=35)	Ratio (D/C)	90% Confidence Interval
ln AUC(0-inf)	426.73	405.80	1.0516	98.96, 111.74
ln AUC(0-t)	370.71	351.14	1.0557	98.88, 112.72
ln Cmax	27.3110	24.4327	1.1178	105.35, 118.60

O-desmethyl Venlafaxine (ODV): Active metabolite

Mean ODV concentrations over time by treatment are presented in the following plot.

Mean ODV Plasma Concentrations Versus Time



A summary of the mean pharmacokinetic parameters and the statistical summary of the pharmacokinetic parameters for ODV are presented in the following tables.

Summary of Pharmacokinetic Parameters of O-desmethyl Venlafaxine for Each Treatment

O-desmethyl Venlafaxine Pharmacokinetic Data
Arithmetic Means (CV%) in 36 Subjects

PK Parameter	N	Venlafaxine HCl 37.5 mg fasted (A)	N	Venlafaxine HCl 37.5 mg fed (B)	N	Effexor XR 37.5 mg fasted (C)
AUC(0-inf) (ng.hr/mL)	36	1508.62(34.49%)	33	1538.28(32.34%)	34	1431.47(31.99%)
AUC(0-t) (ng.hr/mL)	36	1397.00(33.34%)	35	1357.91(35.28%)	35	1301.13(30.59%)
Cmax (ng/mL)	36	47.73(32.39%)	35	45.38(34.26%)	35	44.89(30.37%)
T 1/2 (hr)	36	12.85(19.89%)	33	13.30(19.94%)	34	14.13(20.99%)
Kel (1/hr)	36	0.0571(21.13%)	33	0.0543(21.07%)	34	0.0510(19.56%)
Tmax (hr)	36	12.92(24.01%)	35	12.89(23.86%)	35	11.28(19.19%)

PK Parameter	N	Effexor XR 37.5 mg fed (D)	A/C	B/D	B/A	D/C
AUC(0-inf) (ng.hr/mL)	34	1492.90(35.10%)	1.0538967	1.0290498	1.0183251	1.0429133
AUC(0-t) (ng.hr/mL)	35	1347.40(32.21%)	1.0736774	1.0078019	0.9720226	1.0355594
Cmax (ng/mL)	35	46.18(31.11%)	1.0331086	0.9827572	0.9509103	1.0286578
T 1/2 (hr)	34	14.18(23.06%)	0.895519	0.938996	1.0510187	1.0023549
Kel (1/hr)	34	0.0512(20.34%)	1.1189698	1.0607665	0.9513575	1.0035574
Tmax (hr)	35	11.43(33.30%)	1.1474196	1.127575	0.99787	1.0152284

Comparison of Venlafaxine HCl 37.5 mg fasted (Treatment A) vs. Effexor XR 37.5 mg Fasted (Treatment C)

PK Parameter	Treatment A (N=36)	Treatment C (N=35)	Ratio (A/C)	90% Confidence Interval
ln AUC(0-inf)	1405.39	1325.82	1.0600	101.93, 110.23
ln AUC(0-t)	1301.67	1206.78	1.0786	103.58, 112.32
ln Cmax	44.7810	41.4851	1.0794	103.86, 112.19

Comparison of Venlafaxine HCl 37.5 mg fed (Treatment B) vs. Effexor XR 37.5 mg Fed (Treatment D)

PK Parameter	Treatment B (N=35)	Treatment D (N=35)	Ratio (B/D)	90% Confidence Interval
ln AUC(0-inf)	1377.66	1373.70	1.0029	96.32, 104.41
ln AUC(0-t)	1243.57	1238.81	1.0038	96.36, 104.58
ln Cmax	41.7673	42.3271	0.9868	94.90, 102.60

Comparison of Venlafaxine HCl 37.5 mg fed (Treatment B) vs. Venlafaxine HCl 37.5 mg fasted (Treatment A)

PK Parameter	Treatment B (N=35)	Treatment A (N=36)	Ratio (B/A)	90% Confidence Interval
ln AUC(0-inf)	1377.66	1405.39	0.9803	94.22, 101.98
ln AUC(0-t)	1243.57	1301.67	0.9554	91.74, 99.49
ln Cmax	41.7673	44.7810	0.9327	89.74, 96.94

Comparison of Effexor XR 37.5 mg fed (Treatment D) vs. Effexor XR 37.5 mg fasted (Treatment C)

PK Parameter	Treatment D (N=35)	Treatment C (N=35)	Ratio (D/C)	90% Confidence Interval
ln AUC(0-inf)	1373.70	1325.82	1.0361	99.56, 107.83
ln AUC(0-t)	1238.81	1206.78	1.0265	98.54, 106.94
ln Cmax	42.3271	41.4851	1.0203	98.13, 106.09

Statistical comparison of ODV on log-transformed AUC(0-inf), AUC(0-t) and Cmax for the test treatment vs. reference treatment under fasted conditions resulted in 90% CI for mean ratios within the stipulated range of 80-125%. In comparing the test vs. reference treatments under fed conditions, the 90% CI fell within the stipulated range of 80-125%. For the test and reference treatment, comparison of fed vs fasted conditions resulted in 90% CI for the mean ratios of AUC (0-inf), AUC(0-t) and Cmax within the recommended 90% CI.

Summary of Pharmacokinetic Results: Under fasting conditions the Venlafaxine ER Tablets 37.5 mg formulation (Osmotica Pharmaceutical Corporation) was bioequivalent to Effexor® XR (Venlafaxine HCl) 37.5 mg Extended-Release Capsules. Under fed conditions, the Venlafaxine ER Tablets 37.5 mg formulation (Osmotica Pharmaceutical Corporation) was bioequivalent to Effexor® XR (Venlafaxine HCl) 37.5 mg Extended-Release Capsules.

No significant difference was observed for the test treatment, when comparing fed vs. fasted conditions for venlafaxine and ODV. No significant difference was observed for the reference treatment when comparing fed vs. fasted states for Venlafaxine and O-desmethyl venlafaxine.

Safety Summary: The sponsor reported that the most frequently reported adverse event occurring after receipt of Test-Fasted, Test- Fed, and Reference-Fasted was headache. The most frequently reported adverse events occurring after receipt of Reference-Fed were blood pressure decreased, headache and nausea. The sponsor reported that all treatments were well tolerated. There were no serious or unexpected adverse events reported during this study. The sponsor reported that all adverse events were mild. The sponsor reported that there were no serious or unexpected adverse events reported during this study.

Reviewer's comments: The reviewer agrees with the sponsor's comments.

4.2.4. Study Title (Protocol R04-778): A Relative Bioavailability Study of 225 mg Venlafaxine Hydrochloride Extended-Release Tablets and 225 mg (150 mg and 75 mg) Effexor® XR Capsules Following Multiple Doses

Objective: This study compared the relative bioavailability (rate and extent of absorption) of 225 mg Venlafaxine Hydrochloride Extended-Release Tablets by Osmotica Pharmaceutical with that of 225 mg (1 × 150 mg and 1 × 75 mg) Effexor XR Capsules by Wyeth Pharmaceuticals Inc. following multiple oral doses in healthy adult volunteers.

Study Design: This was a multiple dose, randomized, two-period, two-treatment, two-sequence, crossover study comparing equal doses of test and reference products. The study was conducted with 34 (33 completing) healthy adults. In each study period, seven 225 mg doses were administered to all subjects following the completion of a standardized high fat breakfast (2 eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, 4 ounces of hash brown potatoes and 240 mL of whole milk) 30 minutes prior to dosing every 24 hours for the duration of the study period (7 days). The test formulation was Osmotica Pharmaceutical Corp's 225 mg Venlafaxine Hydrochloride Extended-Release Tablets and the reference formulation was Effexor® XR Capsules (venlafaxine hydrochloride). All doses were administered with 240 mL of water. The subjects received the test product in one study period and the reference product in the other study period. There was a 7 day washout interval between treatments. In each study period, blood samples were collected at pre-dose (0 hour) on Study Day 1, within 15 minutes prior to dose administration on Study Days 5, 6, and 7 and on Study Day 7 at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, and 24. The subjects were allowed to leave the clinical facility after the 24 hour blood sample collection on Study Day 7. The Lot no. for Venlafaxine ER Tablets 225 mg was P535102 and for Effexor XR 150 mg and 75 mg B44162 and B12662, respectively.

Analytical Methods: The concentrations of venlafaxine and D, L-O-Desmethylvenlafaxine in plasma was determined using HPLC/MS/MS method. The standard curve ranged from 3.0 to 500 mg/mL. The method was demonstrated to be specific with no significant baseline interference at the retention times. The between batch accuracy of the QCs ranged from 100.9% to 108.9%. The within- batch accuracy of the QCs ranged from 100.0% to 106.6%. The lower limit of quantitation was 3.0 ng/mL. The between batch precision ranged, expressed as %CV, ranged from 2.08% to 2.95%. The within-batch ranged from 0.46% to 1.38%.

The between batch accuracy of the QCs for desmethyvenlafaxine ranged from 101.3% to 109.4%. The within-batch accuracy of the QCs ranged from 100.5% to 106.5%. The lower limit of quantitation was 3.0 ng/mL. The between batch precision ranged from 2.78% to 3.68%. The within batch CV ranged from 0.9% to 1.38%.
The analytical method is acceptable.

Data analysis: Pharmacokinetic parameters were determined using non-compartmental methods. Analyses for AUC0-t and Cmax were performed on ln-transformed data. For ln-transformed AUC0-t and Cmax estimates of the adjusted differences between treatment means and the standard error associated with these differences were used to construct a 90% confidence interval for the ratio of the test to reference population means. In order to establish bioequivalence under non-fasting conditions, the 90% confidence interval for the ratio of the geometric means between the products should fall within the interval 90-125% for ln-transformed AUC0-t, AUC0-∞, and Cmax.

Results: The following table contains summary of the mean demographic data for all the subjects who participated in the study.

Summary of Mean (±SD) Demographic Data

	All Subjects (N=34)	Males (N=29)	Females (N=5)
Age	26.0 (±8.1)	24.6 (±6.6)	34.0 (±12.1)
Weight (lbs)	178.0 (±30.3)	181.6 (±30.9)	157.0 (±16.1)
Height (in.)	69.5 (±3.1)	70.0 (±2.8)	66.4 (±3.2)
BMI	25.9 (±3.7)	26.0 (±3.9)	25.1 (±2.4)

The following table summarizes the result of the analyses performed on the pharmacokinetic parameters for the test and reference products and the 90% confidence intervals. The individual pharmacokinetic parameters and the descriptive statistics are provided in the Attachment.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Venlafaxine Ln-Transformed Data N=33				
Parameter	Test	Reference	% Ratio	90% CI
$AUC_{0-\tau}$ (ng-hr/mL)	3093.33	2939.84	105.22	(101.16, 109.45)
C_{max} (ng/mL)	198.02	231.73	85.45	(82.26, 88.77)

The 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean are within the 80% and 125% limits for the pharmacokinetic parameters C_{max} and $AUC_{0-\tau}$ of the ln-transformed data.

Safety Summary: The sponsor reported that twenty-one (21) subjects experienced a total of 72 AEs over the course of the study. AEs were mild to moderate in severity. No serious AEs were reported. The sponsor reported than the clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study

exit were considered directly attributable to the product. The sponsor reported that the most frequently reported adverse event (AE) in Treatment A (Venlafaxine ER Tablets 225 mg) was nausea which was reported by 9/34 (26.5%) subjects. Nausea was the most frequently reported AE experienced by subjects in Treatment B (Effexor XR® Extended-Release Capsules 150 mg and Effexor® XR Extended-Release Capsules 75 mg) reported by 12/33 (36.4%) subjects.

Conclusions: For the ln-transformed venlafaxine data, the 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80% to 125% limits. The results indicate bioequivalence between the test and reference products given as a multiple dose under fed conditions.

Reviewer's conclusions: The reviewer agrees with the sponsor's conclusions.

Table 14.4 Summary of Statistical Analysis – Desmethylvenlafaxine-Excluding Subjects 2, 8, 26, and 32 due to Emesis

N=29

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test	Reference	Test	Reference	% Ratio	(Lower Limit, Upper Limit)			
C_{max}	6.022	6.054	412.39	425.71	96.87	(94.54, 99.26)	0.0350	1.0000	5.45
AUC_{0-t}	9.017	9.007	8240.67	8157.92	101.01	(98.84, 103.24)	0.4369	1.0000	4.87

APPEARS THIS WAY ON ORIGINAL

Table 1.1.1
Individual Pharmacokinetic Parameters - Test Product
Venlafaxine

Subject	Sequence	Period	Product	AUC_{0-t} (ng·hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	C_{max}:C_{min} ratio	C_{av} (ng/mL)	$[(C_{max}-C_{min})/C_{av}]$ degree of fluctuation	T_{max} (hr)	T_{half} (hr)	$[(C_{max}-C_{min})/C_{min}]$ Scaling	Ln-Transformed AUC_{0-t}	Ln-Transformed C_{max}
1														
3														
4														
5														
6														
7														
9														
10														
11														
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29														
30														
31														
33														
34														
N				29	29	29	29	29	29	29	29	29	29	29
MEAN				3527.55	216.44	75.85	3.77	146.98	1.06	2.39	13.62	2.77	8.049	5.264
STDEV				1714.74	88.36	48.20	1.80	71.45	0.25	2.54	11.72	1.69	0.51	0.43
% CV				48.61	40.82	63.54	47.85	48.61	24.74	33.60	86.08	61.15	6.28	7.94
MEDIAN				2915.21	194.10	54.74	3.36	121.47	1.09	2.00	24.00	2.28	7.978	5.272

b(4)

Figure 14.1 Mean Plasma Concentration (0-24 hours) - Venlafaxine

N=33

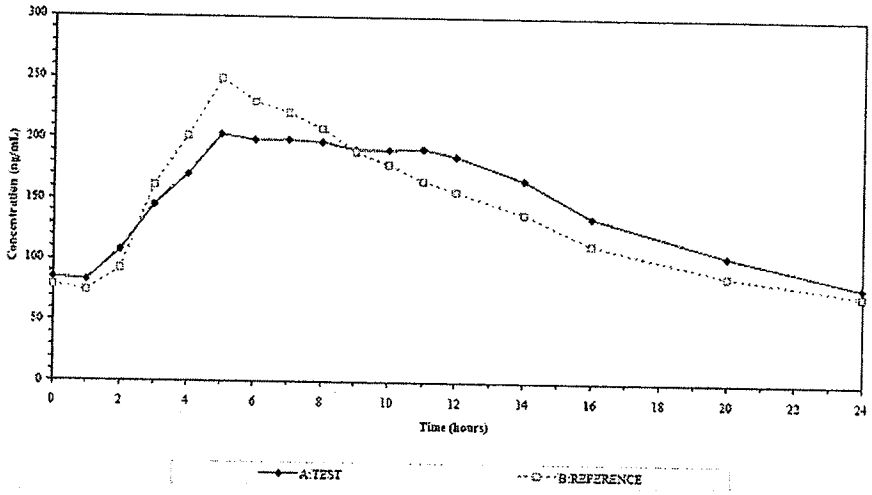

Table 14.2 Summary of Statistical Analysis – Venlafaxine- Excluding Subjects 2, 8, 26, and 32 due to Emesis

N=29

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test	Reference	Test	Reference	% Ratio	(Lower Limit, Upper Limit)			
C_{max}	5.288	5.442	197.89	230.98	85.68	(82.18, 89.32)	<.0001	1.0000	9.33
AUC_{0-t}	8.041	7.978	3105.65	2915.36	106.53	(102.1, 111.15)	0.0173	1.0000	9.51

Table 14.3 Summary of Statistical Analysis - Desmethylvenlafaxine

N=33

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean			90 % Confidence Interval	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test	Reference	Test	Reference	% Ratio	(Lower Limit, Upper Limit)			
C_{max}	6.011	6.039	407.97	419.29	97.30	(95.07, 99.58)	0.0537	1.0000	5.55
AUC_{0-t}	9.007	8.996	8159.96	8073.44	101.07	(99.07, 103.11)	0.3721	1.0000	4.78

Table 12.2
Individual Pharmacokinetic Parameters - Reference Product
Venlafaxine

Subject	Sequence	Period	Product	AUC_{0-t} (ng·hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	C_{max}:C_{ss} C_{max}:C_{min} ratio	C_{av} (ng/mL)	$[(C_{max}-C_{ss})/C_{av}]$ degree of fluctuation	T_{max} (hr)	$T_{1/2}$ (hr)	$(C_{max}-C_{min})/C_{av}$ Swing	Ln-Transformed AUC_{0-t}	Ln-Transformed C_{max}
1														
3														
4														
5														
6														
7														
9														
10														
11														
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27														
28														
29														
30														
31														
33														
34														
				N	N	N	N	N	N	N	N	N	N	N
MEAN				3334.03	250.19	68.78	4.59	139.66	1.48	3.17	12.83	3.53	8.066	4.963
STDEV				1721.06	98.52	47.47	1.56	71.29	0.38	0.97	11.77	1.56	0.52	0.70
% CV				51.26	39.53	69.02	34.79	51.06	24.85	30.68	91.79	44.08	6.46	13.99
MEDIAN				3519.33	222.29	48.08	4.34	112.99	1.41	3.00	24.06	3.54	7.897	5.330
MIN														
MAX														

b(4)

4.2.5. Dissolution Conditions and Specification for Venlafaxine Extended Release Tablet

Dissolution profiles were performed to determine if varying parameters would effect the drug release rate of venlafaxine hydrochloride. The parameters varied included pH, paddle speed, and parameters for comparing the test and reference products using Apparatus II.

A dissolution profile study was performed on Venlafaxine Hydrochloride ER Tablets. For the Apparatus II testing, twelve tablets were placed in 900 mL of media. Samples were taken at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours.

The dissolution media pH was varied with pH 1.2, pH 4.5, pH 6.8, and water, for all four strengths of Venlafaxine Hydrochloride ER Tablets using Apparatus II at 50 rpm. The f2 values are all above 50 which indicate the release was similar in the various media.

The paddle speed was varied for the 37.5 mg and for the 225 mg. The speeds used were 50 rpm, 75 rpm, and 100 rpm and using water as the media. The f2 values are all above 50.

Dissolution Specification
The bio lots have been demonstrated to be bioequivalent to the Effexor XR lots used in the bioequivalence studies. The sponsor states that there are two focal points for the specifications: demonstrating that no dose-dumping occurs and obtaining complete release of the drug.

Based on variations in release rates that would provide products with similar in-vivo performance, the sponsor stated that the ranges were moderately broadened. Based on this rationale, the following specifications were established and proposed by the sponsor:

4 hours: [redacted]
12 hours
20 hours: NLT [redacted]

b(4)

Reviewer comments: The sponsor did not provide adequate data to justify the proposed dissolution specification. The data provided in connection with the in vitro in vivo correlation (IVIVC) development was not sufficient to grant a level A IVIVC for venlafaxine extended release tablets. Based on the dissolution data for bio lots used in the bioequivalence studies and a consideration of the dissolution data for the stability lots, the reviewer proposes the following dissolution method and specification:

Apparatus:	*USP Apparatus II*
Speed:	*50 rpm*
Meida:	*Water*
Volume:	*900 mL*

Specification: Q at

4 hours:		b(4)
12 hours		
20 hours	*NLT*	

The individual dissolution results are provided in the following tables.

Testing Parameters

Test	Product	Lot Number	Strength (mg)	Apparatus	Agitation Speed (rpm)	Media
1	Venlafaxine ER Tablets	P534801	37.5	II	50	pH 1.2 buffer
2	Venlafaxine ER Tablets	P534801	37.5	II	50	pH 4.5 buffer
3	Venlafaxine ER Tablets	P534801	37.5	II	50	pH 6.8 buffer
4	Venlafaxine ER Tablets	P534801	37.5	II	50	water
5	Venlafaxine ER Tablets	P534902	75	II	50	pH 1.2 buffer
6	Venlafaxine ER Tablets	P534902	75	II	50	pH 4.5 buffer
7	Venlafaxine ER Tablets	P534902	75	II	50	pH 6.8 buffer
8	Venlafaxine ER Tablets	P534902	75	II	50	water
9	Venlafaxine ER Tablets	P535002	150	II	50	pH 1.2 buffer
10	Venlafaxine ER Tablets	P535002	150	II	50	pH 4.5 buffer
11	Venlafaxine ER Tablets	P535002	150	II	50	pH 6.8 buffer
12	Venlafaxine ER Tablets	P535002	150	II	50	water
13	Venlafaxine ER Tablets	P535102	225	II	50	pH 1.2 buffer
14	Venlafaxine ER Tablets	P535102	225	II	50	pH 4.5 buffer
15	Venlafaxine ER Tablets	P535102	225	II	50	pH 6.8 buffer
16	Venlafaxine ER Tablets	P535102	225	II	50	water
17	Venlafaxine ER Tablets	P534801	37.5	II	75	water
18	Venlafaxine ER Tablets	P535102	225	II	75	water
19	Venlafaxine ER Tablets	P534801	37.5	II	100	water
20	Venlafaxine ER Tablets	P535102	225	II	100	water
21	Effexor XR	B28534	37.5	II	50	water
22	Effexor XR	B12662	75	II	50	water
23	Effexor XR	B44162	150	II	50	water
24	Effexor XR	B12662 + B44162	75 +150	II	50	water

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X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 4

4.3. DSI Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 23, 2007

TO: Thomas Laughren, M.D., Ph.D., Director,
Division of Psychiatry Products (HFD-13Q)

FROM: Nilufer M. Tampal, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-104, Venlafaxine Hydrochloride Extended Release Tablets, Sponsored by Osmotica Pharmaceutical Corporation.

At the request of HFD-130, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study: R04-0776, A Relative Bioavailability of 225 mg Venlafaxine Hydrochloride Extended Release Tablets and 225 mg (150 mg and 75 mg Effexor® XR) Capsules under Fed Conditions.

The clinical and analytical portions of Study R04-0776 were conducted at Following the inspection of the clinical (7/3-10/07) and analytical (7/9-11/07) portions, Form 483 was issued. Our evaluation of the significant findings is as follows:

1. **Failure to use the same LC/MS/MS acquisition method across all study runs. For example, for study samples reassayed for venlafaxine alone or desmethylvenlafaxine alone were acquired using modified methods that were different from the method used during the study and method validation. Additionally, within the study samples were not acquired using the same acquisition method as the QCs and standards.**

The analytical method was validated to simultaneously acquire data for venlafaxine, desmethylvenlafaxine and the two internal standards (IS) using four channels on the mass

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 5

For future, the management proposed to retain sufficient reserve samples to meet the FDA requirements. This observation does not impact the study outcome.

Conclusions:

Following our evaluation of the inspectional findings, DSI concludes that:

- It is objectionable that the firm modified the LC/MS/MS acquisition parameters of the validated method during subject sample analysis for the sole purpose of not acquiring additional data and without assessing the impact of the change. Because the acquisition parameters for the subject samples in runs ——— were different from the validated method and from the parameters used to acquire the QCs and standards (Run ~ only), the accuracy of the subject sample concentrations in runs ——— cannot be assured by the performance of the QCs (item 1). Data for subject samples listed in table 1 should not be considered for bioequivalence. b(4)

- Accuracy of the concentrations for the QCs and calibration standards used in the study is not assured in the absence of documentation to confirm the stability of venlafaxine and desmethylvenlafaxine in the stock solutions used to prepare the spiked samples (item 3Ia).

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Nilufer M. Tampal, Ph.D.

Final Classification:
VAI - ——— b(4)
cc:
DSI/RF
DSI/Tampal/Himaya/CF
DSI/Vaccari
OND/ODEI/DNP/Bender
HFR-CE300/Holaday
HFR-CE850/Sharon Matson
Draft: NMT 7/16/07
Edit: JAO, SS 7/20/07
DSI: —— O:\BE\eircover\22104osm.ven.doc b(4)
FACTS: ——

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On Original

Table 1.

Subject samples from — analyzed using b(4)
acquisition parameters different from the validated method.

S.No.	Run #	Sample I.D. Subject-period-time point	Reassayed for
1		15-1-20	venlafaxine
2		15-2-1	venlafaxine
3		15-2-2	venlafaxine
4		15-2-20	venlafaxine
5		16-1-2	venlafaxine
6		18-1-20	venlafaxine
7		18-2-1	venlafaxine
8		18-2-2	venlafaxine
9		20-2-1	venlafaxine
10		11-1-8	desmethylvenlafaxine
11		11-1-9	desmethylvenlafaxine
12		11-1-10	desmethylvenlafaxine
13		11-1-11	desmethylvenlafaxine
14		11-1-12	desmethylvenlafaxine
15		11-1-13	desmethylvenlafaxine
16		11-1-14	desmethylvenlafaxine
17		11-1-15	desmethylvenlafaxine
18		18-1-8	desmethylvenlafaxine
19		18-2-11	desmethylvenlafaxine
20		18-2-12	desmethylvenlafaxine
21		18-2-13	desmethylvenlafaxine
22		18-2-14	desmethylvenlafaxine
23		18-2-15	desmethylvenlafaxine
24		20-1-14	desmethylvenlafaxine
25		20-2-11	desmethylvenlafaxine
26		20-2-12	desmethylvenlafaxine
27		20-2-13	desmethylvenlafaxine
28		20-2-14	desmethylvenlafaxine
29		20-2-15	desmethylvenlafaxine
30		32-1-10	desmethylvenlafaxine
31		32-1-11	desmethylvenlafaxine
32		32-1-12	desmethylvenlafaxine
33		32-1-13	desmethylvenlafaxine
34		32-1-14	desmethylvenlafaxine
35		32-2-12	desmethylvenlafaxine
36		32-2-13	desmethylvenlafaxine
37		35-1-1	desmethylvenlafaxine

b(4)

S.No.	Run #	Sample I.D. Subject-period-time point	Reassayed for
38		35-2-1	desmethylvenlafaxine
39		35-2-2	desmethylvenlafaxine
40		36-1-1	desmethylvenlafaxine
41		36-1-2	desmethylvenlafaxine
42		36-1-3	desmethylvenlafaxine
43		36-2-1	desmethylvenlafaxine
44		36-2-2	desmethylvenlafaxine
45		36-2-3	desmethylvenlafaxine

b(4)

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/s/

Nilufer Tampal
7/25/2007 04:29:03 PM
PHARMACOLOGIST
Dr. Viswanathan signed the paper copy on 7/24/07 and is available upon request.

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/s/

Kofi Kumi
9/24/2007 02:17:18 PM
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Raman Baweja
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Mehul Mehta
9/25/2007 12:10:10 PM
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