CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAR _7 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,699 **Submission Date:** May 16, 1996
November 20, 1996
IND date: January 28, 1996

Drug Name and Formulation: Effexor-XR® (Venlafaxine) extended release capsules, 37.5, 75, 100 and 150 mg strengths

Sponsor: Wyeth Ayerst Research, Philadelphia, PA 19101

DETIQN
MAR 07 1997

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application

SYNOPSIS: Venlafaxine hydrochloride is a structurally novel antidepressant currently available as an immediate release tablet, Effexor (to be administered twice or three times a day). The sponsor developed an extended release capsule formulation of Effexor, which is the subject of this application. This is proposed for treatment of depression, including depression with associated anxiety, and for the relief of symptoms of anxiety in depressed patients with associated anxiety. Effexor XR extended release capsules are a once-a-day treatment for depression that consist of encapsulated spheroids which release venlafaxine by diffusion through a slow dissolving coating mechanism. The sponsor submitted this NDA to gain approval of an extended release capsule formulation of venlafaxine (Effexor XR) in 4 dosage strengths of 37.5, 75, 100 and 150 mg. The proposed usual dose of venlafaxine XR is 75 mg to be taken once a day. The NDA contains several pharmacokinetic and clinical studies.

13 in-vivo studies have been submitted. Four studies have not been reviewed because those formulations were not relevant to the ones used in the study and / or proposed for marketing.

The sponsor has adequately validated the assay methodology for venlafaxine. The sponsor also adequately characterized the pharmacokinetics (single and multiple dose) of venlafaxine administered as Effexor-XR. The relative bioavailability, of the 75 mg and 150 mg to-be marketed capsules have been determined following both single dose and at steady state, in comparison to the conventional approved formulation and to the 75 mg formulation that has been used in clinical trials. The to-be marketed formulation is identical to that of the clinical trial formulation, but will be manufactured at a different site, AWPI, Puerto Rico instead of NY.

When the three ER formulations, 150 mg ER (PR), 75 mg ER (PR) and 75 mg ER (NY), were compared to the approved immediate release tablet, the AUC for venlafaxine and ODV (and the composite) were within the confidence interval criteria of 80 - 125%. Fluctuation index for all ER products was separately shown to be less than the fluctuation index for the immediate release formulation for venlafaxine and the composite, and was comparable for ODV.

The 150 mg ER capsule (PR) and the 75 mg ER capsule (PR) met the bioequivalence criteria, in comparison to 75 mg venlafaxine ER (NY) formulation (the clinical trial formulation) as reference, with respect to C_{max}, C_{min} & AUC_{24} (and R_{ss}). In addition, the mean t_{max} for the two ER treatments were similar for venlafaxine and ODV.

There was no food effect on the bioavailability of the 150 mg ER to-be marketed highest strength formulation as well as the 75 mg clinical trial ER formulation.

The 37.5 and 100 mg ER strengths that have also been proposed for marketing have not been evaluated for bioavailability. A biowaiver can be granted for these two strengths, since they are compositionally proportional, venlafaxine and its active metabolite, ODV, are known to exhibit linear kinetics up to 450 mg/day, and that these formulations have comparable in vitro dissolution profiles to the 75 and 150 mg strengths.

The sponsor has also conducted a multiple dose study to evaluate the effect of AM versus PM administration of venlafaxine XR capsules. Results show that there is no diurnal variation in venlafaxine pharmacokinetics and Effexor XR can thus be administered either in the morning or in the evening as long as it is administered at the same time each day.

In vitro and in vivo studies indicate that cytochrome P450 2D6 isoenzyme is involved in the metabolism of venlafaxine to its active metabolite, O-desmethylvenlafaxine (ODV). When venlafaxine is administered concomitantly with imipramine, the AUC, C_{max} and C_{min} of the active metabolite, desipramine increased by about 35%. Further, the 2-OH desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not inhibit the metabolism of venlafaxine to ODV.

RECOMMENDATION: The present submission (NDA 20-699) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The submission is acceptable for the 37.5, 75, 100 and 150 mg strengths of Effexor XR capsules provided the sponsor adopts dissolution specifications as outlined in comment # 1 to sponsor, and incorporates labeling as outlined in Appendix A.

Please forward the above recommendation, and comments to the firm.

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Appendix I (Study summaries)

I. BACKGROUND

Venlafaxine hydrochloride is a structurally novel antidepressant currently available as an immediate release tablet, Effexor (to be administered twice or three times a day). Venlafaxine is a bicyclic ethylamine derivative, administered as a racemate, that acts as a potent inhibitor of neuronal uptake of norepinephrine, serotonin and dopamine. The active ingredient venlafaxine is designated

as (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride. Venlafaxine and its active metabolite, ODV are equipotent in activity.

The sponsor developed an extended release formulation of Effexor, which is the subject of this application. Effexor XR will be manufactured at Ayerst-Wyeth Pharmaceutical, Puerto Rico. This is proposed for treatment of depression, including depression with associated anxiety, and for the relief of symptoms of anxiety in depressed patients with associated anxiety. Effexor XR extended release capsules are a once-a-day treatment for depression that consist of encapsulated spheroids which release venlafaxine by diffusion through a slow dissolving coating mechanism. The sponsor submitted this NDA to gain approval of an extended release capsule formulation of venlafaxine (Effexor XR) in 4 dosage strengths of 37.5, 75, 100 and 150 mg. The proposed usual therapeutic dose is 75 mg/day. Patients may be started at 37.5 mg/day which can be increased to 75 mg/day up to a maximum of 300 mg/day to be taken once daily with food.

II. FORMULATION:

The details of formulation for the four strengths of Effexor XR formulation are given below.

COMPOSITION OF EFFEXOR XR CAPSULES

INGREDIENTS	37.5 mg strength	75 mg strength	100 mg strength	150 mg strength
Venlafaxine hydrochloride (at 88.4% of base)	42.43 mg	84.85 mg	113.1 mg	169.7 mg
Microcrystalline cellulose, NF				
Hydroxypropylmethylcellulose, 2208 USP, 3 cps				
Hydroxypropylmethylcellulose, 2910 USP, 6 cps				
Ethylcellulose, NF, HG2834, 50 cps				
Hard gelatin capsule (*#3 opaque light grey cap and*				

** The ER properties are obtained due to these ingredients. The actual quantities used may vary from batch to batch, and must be sufficient to produce spheroids that meet the in-process target in vitro dissolution specifications.*

III. STUDIES THAT WERE EITHER NOT REVIEWED OR WERE ONLY BRIEFLY REVIEWED:

Several studies have been submitted as part of the NDA, however, studies that are not pivotal will not be included in this review. List of studies not reviewed with reasons are provided below.

IV. PHARMACOKINETICS:

The summary of pharmacokinetics of the drug obtained from Effexor XR capsule and from the immediate release submitted in this NDA is provided below:

a. SINGLE DOSE PHARMACOKINETICS: Absolute bioavailability of venlafaxine is approximately 40 and 45% for the ER and IR formulations respectively.

In the pivotal single dose bioequivalence study performed with food (study 143), a single oral dose of 2 x 75 mg venlafaxine ER (NY) was compared to a single oral dose of 1 x 150 mg venlafaxine ER (PR) and to a single oral dose of 1 x 50 mg venlafaxine IR. The dose-normalized venlafaxine and ODV C_{max} following the two ER treatments were lower than that of the IR treatment due to a slower rate of absorption. However, the venlafaxine and ODV AUC met the equivalence criteria (C.I. for venlafaxine AUC = 87 - 101 (and 84 - 93 for ODV) for the 75 mg ER (NY) clinical trial formulation and 83 - 96 (and 86 - 95 for ODV) for the 150 mg PR to-be marketed formulation in comparison to the conventional formulation as reference).

The 150 mg ER capsule (to-be marketed; PR) is bioequivalent to the 2 x 75 mg venlafaxine ER (NY) formulation which has been used in clinical trials (90% confidence intervals for venlafaxine AUC = 89 - 103 (and 97 - 108 for ODV); C_{max} = 87 - 104 (and 87 - 123 for ODV)). In addition, the mean t_{max} for the two ER treatments were similar for venlafaxine, 6 hours and ODV, 11 hours.

b. MULTIPLE DOSE PHARMACOKINETICS: In the pivotal multiple dose bioequivalence study (study 136) performed with food, comparisons were made between multiple oral dose regimens of 2 x 75 mg venlafaxine ER (NY) (I), 2 x 75 mg venlafaxine ER (PR) (II), 1 x 150 mg venlafaxine ER (PR) (III) and 75 mg venlafaxine IR q12 hours. All 3 venlafaxine ER formulations produced lower steady state venlafaxine C_{max} and similar steady state venlafaxine C_{min} and AUC_{24} to that of the 75 mg conventional IR Q12h treatment. The 3 ER formulations produced similar steady state ODV C_{max}

C_{min} and AUC_{24h} to that of the 75 mg IR treatment.

When the three ER formulations were compared to the approved CF tablet, the AUC for venlafaxine and ODV (and the composite) were within the confidence interval criteria of 80 - 125%. Fluctuation index for all ER products was separately shown to be less than the fluctuation index for the CF (immediate release) formulation for venlafaxine and the composite, and was comparable for ODV.

The 150 mg ER capsule (PR) and the 75 mg ER capsule (PR) met the bioequivalence criteria, in comparison to 75 mg venlafaxine ER (NY) formulation as reference, with respect to C_{max}, C_{min}, & AUC_{24} ([redacted]). In addition, the mean t_{max} for the two ER treatments were similar for venlafaxine and ODV.

c. FOOD EFFECT: Food did not affect the rate and extent of absorption of venlafaxine or the rate and extent of formation of ODV from either the 150 mg ER or 75 mg venlafaxine ER capsules. Two single dose studies were conducted to study the effect of food. The first study (145) was carried out using the 150 mg (highest strength) to-be marketed formulation. The presence of food (high fat meal) did not significantly affect the absorption or disposition of either venlafaxine or ODV. The mean (and 90% confidence interval) relative bioavailability of fed with respect to fasted state was 99% (92 - 107) and 99% (93 - 105) for venlafaxine and ODV, respectively. The corresponding C_{max} ratios were 99 and 103% for venlafaxine and ODV. Therefore, administration with high fat meal did not produce a dose-dumping effect on the 150 mg venlafaxine ER capsule.

The second study (138) was carried out using the 75 mg ER clinical trial formulation. The presence of food (high fat meal) did not significantly affect the absorption or disposition of either venlafaxine or ODV. The mean (and 90% confidence interval) relative bioavailability of fed with respect to fasted state was 96% (87 - 107) and 101% (93 - 109) for venlafaxine and ODV, respectively. The corresponding C_{max} ratios were 101 and 107% for venlafaxine and ODV.

d. DIURNAL VARIATION: Time of administration (AM vs. PM) did not affect the rate or extent of absorption of venlafaxine or the rate and extent of formation of ODV from the 75 mg venlafaxine ER capsule (study 139). The AM vs PM geometric mean ratios for C_{max} and AUC were 97 and 104% for venlafaxine and 96 and 100% for ODV. Therefore, patients being treated with venlafaxine ER may take their daily dose of venlafaxine ER either in the morning or evening, provided they take it at approximately the same time each day.

e. DRUG INTERACTIONS AND IN VITRO METABOLISM:

In vitro metabolism: In vitro studies of metabolism of venlafaxine in human liver microsomes, and chemical inhibition methods indicate that venlafaxine is metabolized by cytochrome P450 2D6 to its active metabolite, ODV. Involvement of CYP3A4 in metabolism of venlafaxine to N-desmethylvenlafaxine has been claimed in vitro by the sponsor. However, this study was conducted using very high concentrations of venlafaxine enantiomers (100 μM). Since these concentrations are much higher than the maximum plasma concentrations of venlafaxine achieved normally in humans, the study is not confirmatory.

Imipramine (study 129):
EFFECT OF VENLAFAXINE ON IMIPRAMINE: Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in presence of venlafaxine. The 2-OH desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h).
EFFECT OF IMIPRAMINE ON VENLAFAXINE: Imipramine does not affect the pharmacokinetics of venlafaxine and ODV.
Effect of genetic polymorphism (study 131): Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. However, the total exposure to the sum of the equipotent parent and ODV was similar in both poor and extensive metabolizer groups. Hence, pharmacokinetically, there is no basis for different venlafaxine dosing regimens for these two groups.

V. DISSOLUTION: In vitro dissolution tests were conducted on 12 individual units from at least 3 batches of the proposed marketing strengths of venlafaxine ER capsules (37.5, 75, 100 and 150 mg). The method used was

In vitro/In vivo correlation: A level A IVIVC has been established for Effexor XR capsules. The IVIVC development study was a crossover design study conducted in 14 subjects under fed conditions using 3 ER formulations, slow, medium and fast (75 mg strength, study 127). Its external predictability has been evaluated using data from the pivotal single dose study (143) and predictions were carried out for both 75 mg ER and 150 mg ER strengths.

Waiver of 37.5 and 100 Mg Strengths That Were Not Used in Clinical Trials/Bioavailability Studies: The 75 and 150 mg Effexor XR strengths were used in bioavailability studies. However, the 37.5 and 100 mg strengths were not studied in vivo. A biowaiver can be granted for these two strengths, since they are compositionally proportional, venlafaxine and its active metabolite, ODV, are known to exhibit linear kinetics up to 450 mg/day, and that these formulations have comparable in vitro dissolution profiles to the 75 and 150 mg strengths.

COMMENTS TO THE MEDICAL OFFICER:

1. The decision of equivalence between Effexor-XR extended release capsule formulations and Effexor immediate release tablet formulation was based on criteria on the individual moieties, venlafaxine (V) and O-desmethylvenlafaxine (ODV). Although the composite (V + ODV) was evaluated, it was not used to conclude equivalence.

2. Coadministration of venlafaxine with imipramine resulted in a 35% increase in plasma concentrations of desipramine, the active metabolite of imipramine. Further, the 2-OH desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h).

3. The sponsor claims that there is an involvement of CYP3A4 in metabolism of venlafaxine to N-desmethylvenlafaxine in vitro. However, this study was conducted using very high concentrations of venlafaxine enantiomers (100 μM). Since these concentrations are much higher than the maximum plasma concentrations of venlafaxine achieved normally in humans, this study does not confirm the enzymatic role of CYP3A4.

4. Under 'Drug interactions' section of the label, the sponsor has changed the presentation from *'50 mg q8 hours'* to *'150 mg/day'*, thus omitting the details of the dosing interval.

5. Under Precautions/Drug interactions/Cimetidine, the sponsor has included a new sentence 'Therefore, cimetidine apparently inhibited the formation of minor, inactive metabolites via inhibition of CYP3A3/4'. This has not been substantiated.

6. OCPB labeling is being provided in the attached Appendix A.

COMMENTS TO THE SPONSOR:

1. The dissolution method is acceptable. Based on the dissolution data provided, the following specifications should be adopted by the sponsor for all strengths of Effexor XR capsules:

Specifications:

TIME	RANGE (% DISSOLVED)
2	
4	
8	
12	
20	

2. This NDA has been compiled well in terms of all the studies and the information that was provided. Sponsor also provided information on dissolution for the 37.5 and 100 mg strengths in a timely manner upon request from the reviewer.

03/05/97

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation-I

Clin. Pharm/Biopharm. Briefing 03/03/97 (J.Balian, R.Baweja, S.Blum, M.Chen, G.Dubitsky, S.Huang, J.Jenkins, T.Laughren, P.Leber, L.Lesko, H.Malinowski, M.Mehta).

FT Initialed by R. Baweja, Ph.D. Rama Baweja 3/7/97

CC list: HFD-120: NDA 20,699; HFD-120: Division file; HFD-120: CSO; HFD-860: Biopharm\Ray Baweja; HFD-860: Biopharm\Mehul Mehta; HFD-860: Biopharm\Malinowski; HFD-850: Mira Millison; HFD-860: Biopharm\Venkata Ramana S. Uppoor; HFD-340: Viswanathan.

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APPENDIX A
OCPB SUGGESTED LABELING

The following labeling information in italics is new for venlafaxine based on new information provided in the Effexor XR NDA.

PHARMACOKINETICS

Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively.

ABSORPTION

Venlafaxine (V) is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. *The absolute bioavailability of venlafaxine is about 45%.* When equal daily doses of venlafaxine immediate release tablets were administered as either b.i.d. or t.i.d. regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Administration of Effexor-XR (150 mg q24 hours) generally resulted in lower C_{max} for both venlafaxine (150 ng/ml) and ODV (260 ng/ml) which are attained at later times (T_{max} for V = 5.5 hours and for ODV = 9 hours) than immediate release venlafaxine tablets (C_{max} with immediate release 75 mg q12 hours, for V and ODV = 225 and 290 ng/ml; T_{max} for V and ODV = 2 and 3 hours). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower following treatment with the Effexor XR capsule. Therefore, Effexor XR extended release capsules provide a slower rate of absorption with comparable extent of absorption, as the immediate release Effexor tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs. PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg venlafaxine ER capsule.

DISTRIBUTION

The degree of binding of venlafaxine to human plasma proteins is 27%±2% at concentrations ranging from 2.5 to 2215 ng/mL, and the degree of ODV binding to human plasma proteins is 30%±12% at concentrations ranging from 100 to 500 ng/mL. *These concentrations of V and ODV studied include therapeutically achievable concentrations.* Protein-binding induced drug interactions with venlafaxine are not expected.

METABOLISM

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver. The primary metabolite of venlafaxine is ODV, but venlafaxine is also metabolized to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6 and this has been confirmed in a clinical study involving extensive and poor metabolizers of CYP2D6.*

EXCRETION

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours after a single radiolabeled dose as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%), and 92% of the radioactive dose is recovered within 72 hours. Therefore, renal elimination of venlafaxine and its metabolites is the primary route of excretion.

SPECIAL POPULATIONS

Age and Gender: A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered due to age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see "DOSAGE AND ADMINISTRATION).

Extensive/Poor metabolizers: *Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. However, the total AUC of V and ODV was similar in both poor and extensive metabolizer groups. Hence, pharmacokinetically, there is no basis for different venlafaxine dosing regimens for these two groups.*

Liver Disease: In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. Dosage adjustment is necessary in these patients (see "DOSAGE AND ADMINISTRATION").

Renal Disease: In a renal impairment study, venlafaxine elimination study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR = 10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR = 10-70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56%, compared to normal subjects. A large

degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see "DOSAGE AND ADMINISTRATION").

PRECAUTIONS/DRUG INTERACTIONS

Venlafaxine-imipramine:

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in presence of venlafaxine. The 2-OH desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h).

Imipramine did not affect the pharmacokinetics of venlafaxine and ODV.

Dosage and Administration

Effexor XR should be administered once daily with food and can be taken either in the morning or evening, provided that it is taken at approximately the same time each day.

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APPENDIX I

STUDY 600-B-127-US: PILOT SINGLE DOSE COMPARATIVE BIOAVAILABILITY STUDY

A COMPARATIVE BIOAVAILABILITY STUDY OF THREE SUSTAINED-RELEASE FORMULATIONS AND THE CONVENTIONAL FORMULATION OF VENLAFAXINE

Reference: Volumes 17 and 18
Investigator:
Study Location:

Objective:

To evaluate the relative bioavailability of three different 75 mg sustained release formulations of venlafaxine as compared with a 75 mg dose (37.5 mg q12 hours) of the conventional formulation.

Study design:

This is a pilot, open-label, randomized, four-way crossover study of single doses of 75 mg of 3 formulations of venlafaxine ER capsules compared to the conventional formulation of venlafaxine (IR) 37.5 mg taken q12 hours. 16 healthy male volunteers of age 18 - 45 years participated in the study (14 completed the entire study). The four assessment periods were separated by a 5 to 7 day washout period.

Study drug:
37.5 mg venlafaxine conventional tablet formulation; batch # 2TCC/2TCC1, batch size
1. Venlafaxine ER 75 mg capsule, single dose, batch #2TJN/2TJN1, batch size
2. Venlafaxine ER 75 mg capsule, single dose, batch #2TJP/2TJP1, batch size
3. Venlafaxine ER 75 mg capsule, single dose, batch #2TJQ/2TJQ1, batch size

Subjects reported to the study site the evening before the dosing day. At about 8 a.m. on the dosing days, within 30 minutes of a standardized high fat breakfast, each subject received either one of the three venlafaxine ER capsules or a single dose of the 37.5 mg venlafaxine conventional formulation along with 240 ml of water. The subjects who received a single 37.5 mg dose of the venlafaxine conventional formulation received an additional 37.5 mg dose at about 8 p.m. Additional meals and snacks were served at noon, 4 p.m. and 7.30 p.m. Hence, all venlafaxine doses were administered after a meal.

The standardized high fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 pieces of toast with butter, 4 oz of hashbrown potatoes cooked in butter and 8 oz of whole milk.

Blood was collected for determination of plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine at 0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 36 and 48 hours after dose administration for the 75 mg venlafaxine ER formulations. For the conventional formulation, blood samples were drawn at 0, 0.5, 1, 2, 4, 6, 8, 12, 12.5, 13, 14, 16, 20, 24, 28, 36,

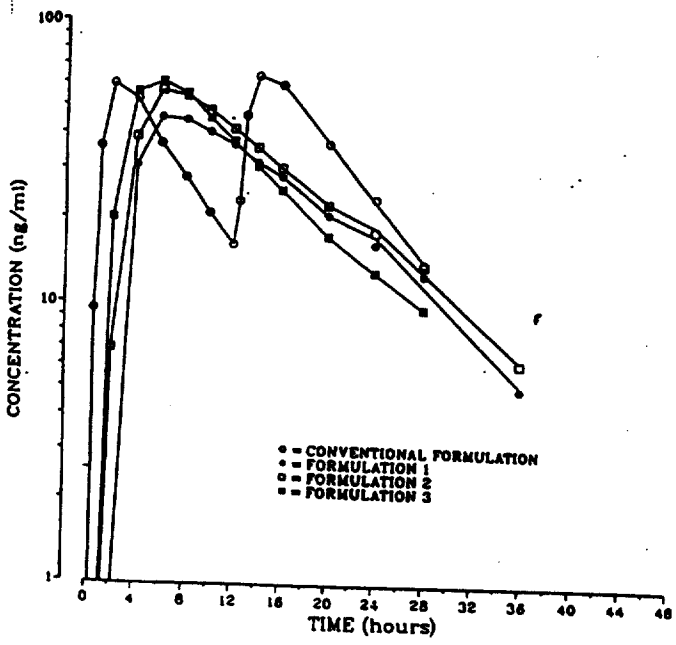
and 48 hours after dosing. Following a pre-dose void, complete urine output was collected from 0-12, 12-24 and 24-48 hours after dose administration for all treatment groups. Pharmacokinetic analysis of data was performed using model-independent techniques. The Wagner-Nelson deconvolution method was used to evaluate the cumulative fraction of venlafaxine absorbed as well as the cumulative amount of ODV formed at each time point. Statistical comparisons of the mean estimates of PK parameters among the 4 treatments were made by using an ANOVA for a four-period crossover design.

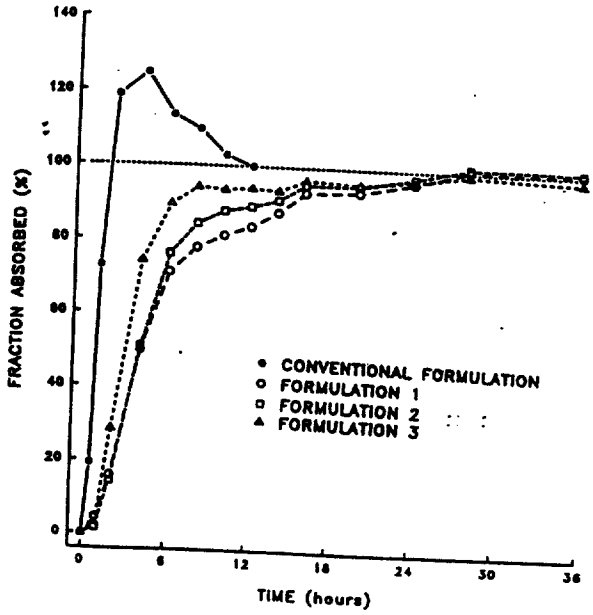
Results:

ASSAY PERFORMANCE: Assay conducted at

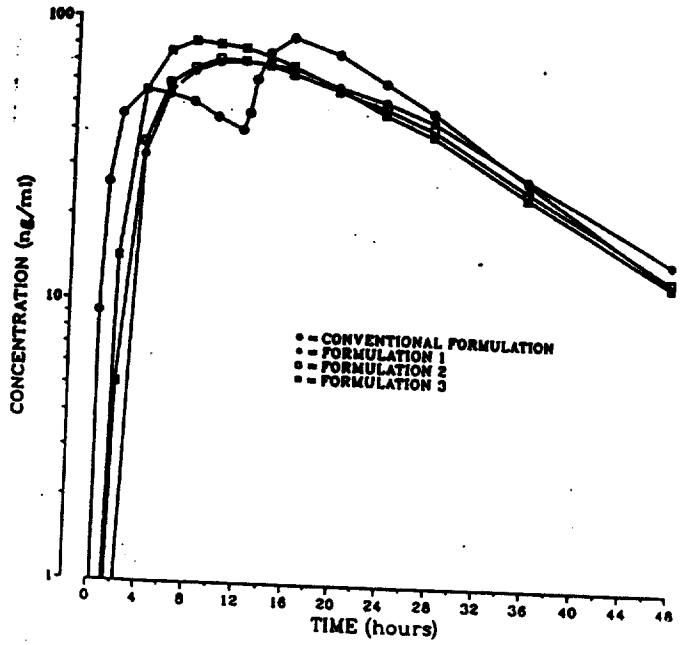
Assays for venlafaxine and ODV were found to be acceptable.

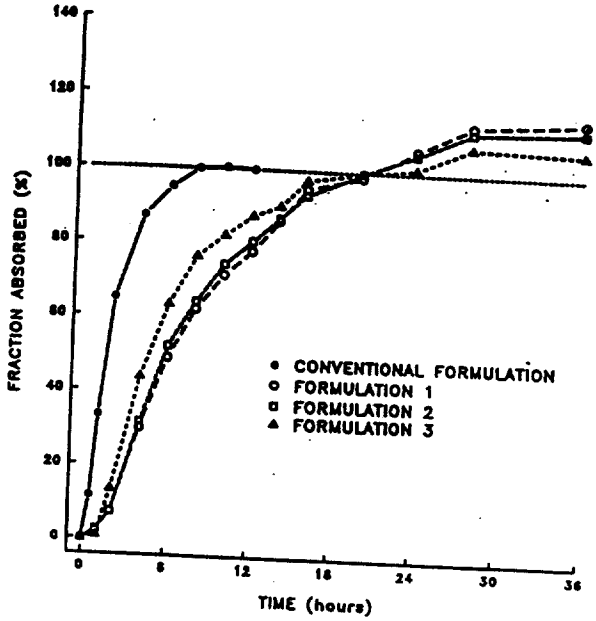
Mean plasma concentration-time curves and the mean fraction of drug absorbed-time curves of venlafaxine after administration of the 3 venlafaxine ER capsules and the conventional venlafaxine tablet are shown in the following figures.





Mean plasma concentration-time curves and the mean fraction of metabolite formation-time curves of ODV after administration of the 3 venlafaxine ER capsules and the conventional venlafaxine tablet are shown in the following figures.





The mean C_{max} for venlafaxine and ODV was lower and was attained later for each of the 3 sustained release formulations than the conventional formulation. Similarly, the mean t_{90} was considerably longer for the sustained release formulations than for the conventional formulation.

A summary of venlafaxine PK parameters (mean ± std. dev.) and the relative bioavailability, based on AUC and amount excreted in urine along with 90% confidence intervals, following administration of the four formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	t_{max} (hours)	$t_{1/2}$ (hours)	AUC (ng.hr/ml)	Rel. Bioav - % AUC (C.I.)	Rel. Bioav -% A_e (C.I.)	t_{90} (h)
37.5 mg bid IR	76 ± 26	2.3 ± 1.2	6.4 ± 2.4	1167 ± 590			1.5 ± 0.6
ER formln. #1	47 ± 17	7.3 ± 2.3	11.8 ± 2.8	964 ± 415	91 (89 - 93)	98 (90 - 106)	16.2 ± 5.2
ER formln. #2	58 ± 22	6.3 ± 1.0	9.9 ± 1.7	1056 ± 529	90 (88 - 92)	89 (83 - 95)	12.7 ± 6.6
ER formln. #3	65 ± 25	5.4 ± 1.5	9.6 ± 2.1	979 ± 428	91 (89 - 93)	106 (99 - 114)	8.3 ± 6.3

A summary of ODV PK parameters (mean ± std. dev.) and the relative bioavailability, based on AUC and amount excreted in urine along with 90% confidence intervals, following administration of the four formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	t_{max} (hours)	$t_{1/2}$ (hours)	AUC (ng.hr/ml)	Rel. Bioav - % AUC (C.I.)	Rel. Bioav -% A_e (C.I.)	t_{90} (h)
37.5 mg bid IR	87 ± 25	3.5 ± 1.7	10.4 ± 2.0	2328 ± 713			4.9 ± 1.9
ER formln. #1	73 ± 16	12.0 ± 2.8	13.1 ± 3.3	2290 ± 432	95 (91 - 101)	97 (81 - 116)	15.5 ± 3.8
ER formln. #2	74 ± 21	11.8 ± 2.9	12.2 ± 2.3	2208 ± 583	94 (90 - 98)	90 (76 - 106)	14.7 ± 2.2
ER formln. #3	83 ± 20	8.7 ± 2.2	11.8 ± 2.0	2223 ± 382	93 (89 - 97)	103 (86 - 122)	14.0 ± 4.2

Since venlafaxine and ODV have similar activity and are equipotent, composite PK parameters can be estimated. A summary of composite (venlafaxine + ODV) AUC (mean ± std. dev.) and the relative bioavailability, based on AUC along with 90% confidence intervals, following administration of the four formulations are presented in the following table:

Treatment	AUC (ng.hr/ml)	Rel. Bioav - % AUC	90% C.I.
37.5 mg bid IR	3495 ± 619		
ER formln. #1	3254 ± 535	93	90 - 97
ER formln. #2	3264 ± 478	93	90 - 96
ER formln. #3	3202 ± 457	92	89 - 96

Conclusion: Absorption of venlafaxine was slower with all the 3 ER formulations than the conventional formulation. The total exposure to active species (venlafaxine and ODV) from the 3 ER formulations was equivalent to that from the conventional formulation. Thus, any of these 3 formulations can be selected for further development.

Comments:

Formulation 2, i.e. the 75 mg venlafaxine ER capsule (batch # 2TJP/2TJP1) with a t_{90} of 12.7 hours has been selected for further development work by the sponsor.

STUDY 600-B-143-UK: PIVOTAL SINGLE DOSE COMPARATIVE BIOAVAILABILITY STUDY

A SINGLE-DOSE RELATIVE BIOAVAILABILITY STUDY OF TWO EXTENDED RELEASE (75 mg ER and 150 mg ER) AND ONE CONVENTIONAL FORMULATION (50 mg) OF VENLAFAXINE IN HEALTHY ADULT VOLUNTEERS

Reference: Volumes 25 and 26
Investigator:
Study Location:

Objective:

1. To evaluate the relative bioavailability of a single 150 mg dose of venlafaxine given as either two 75 mg extended release capsules manufactured in New York (NY) or one 150 mg ER capsule manufactured in Puerto Rico (PR).
2. To compare the pharmacokinetic profiles of the ER formulations with the profile of a market 50 mg conventional formulation (CF) tablet (placed in a capsule) (Reference).

Study design:

This is a randomized, open-label, 3-period crossover study of single doses of 150 mg venlafaxine given as either 150 mg ER capsule (made in PR) or 2x75 mg ER capsule (made in NY) or one venlafaxine 50 mg immediate release tablet (placed in a capsule). 24 healthy volunteers (12 male and 12 female) participated in the study. Each assessment period was separated by at least a 5 day washout period.

Study drug: Venlafaxine ER 75 mg capsule (NY), batch # 3THV, batch si:
Venlafaxine ER 150 mg capsule (PR), batch #A94D018/3TJB, batch size
Venlafaxine 50 mg tablet in a capsule, batch #4WES, batch size

Subjects reported to the study site the evening before the dosing day. At about 8 a.m. on the dosing days, within 30 minutes of a standardized high fat breakfast, each subject received either one of the two venlafaxine ER capsule treatments (2 x 75 mg or 1 x 150 mg) or a single dose of the 50 mg venlafaxine conventional formulation.

The standardized high fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 pieces of toast with butter, 4 oz of potatoes fried in butter, 4 oz of whole milk, 2 packets of sugar, 1 cup of decaffeinated coffee and 4 oz of water.

Blood was collected for determination of plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 36, 48 and 72 hours after each dose. Pharmacokinetic analysis of data was performed using model-independent techniques. $AUC_{0-\infty}$ and C_{max} were log transformed before analysis. These endpoints were analyzed using an ANOVA model allowing for effects of subjects within sequence, sequence, period and

treatment as factors in the model to identify any significant treatment differences. Assessments of the magnitude of difference between the two treatments were made with the two one-sided test procedure applied to log-transformed data. For the purpose of bioequivalence testing, the two 75 mg ER capsules served as the reference formulation, and the 150 mg ER capsule was considered the test formulation. The 50 mg tablet was used as a general reference for both ER formulations.

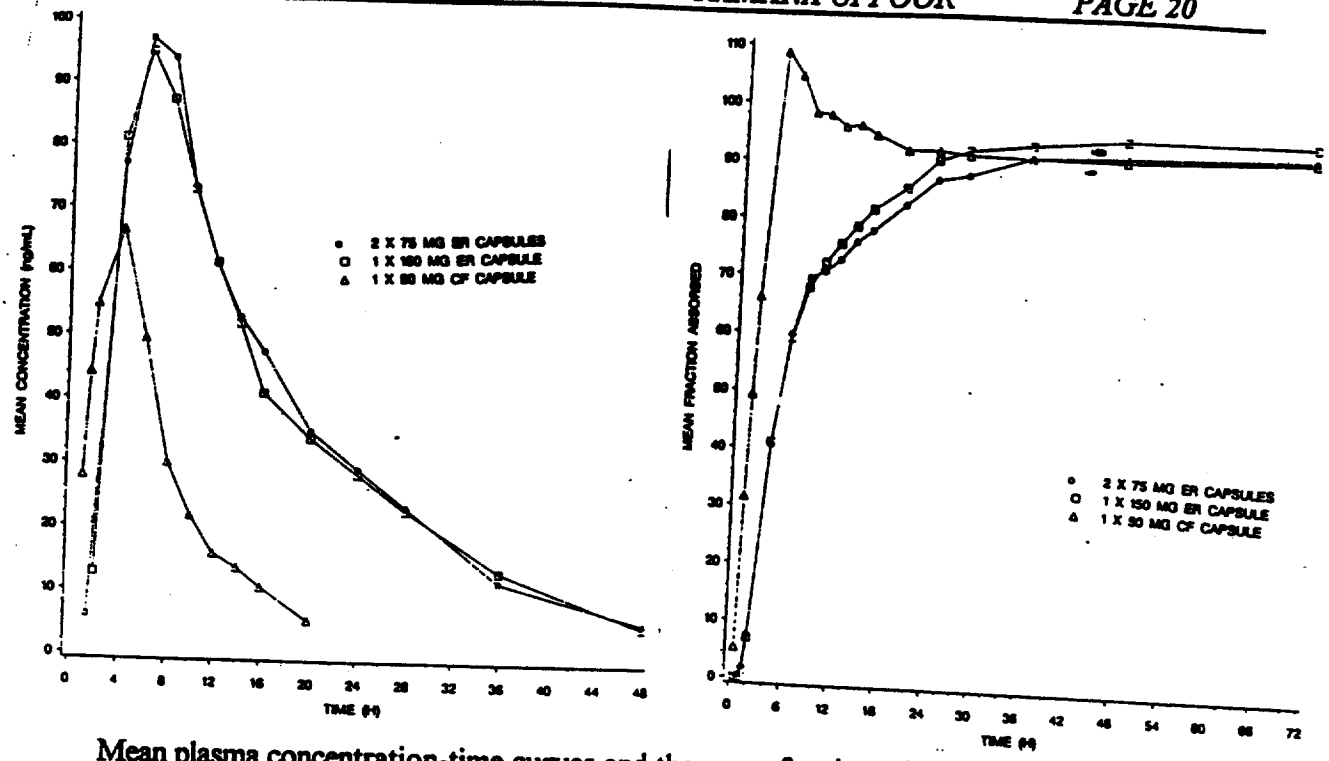
Additionally, the Wagner-Nelson deconvolution method was applied to determine the absorption profile of the 3 formulations.

Results:

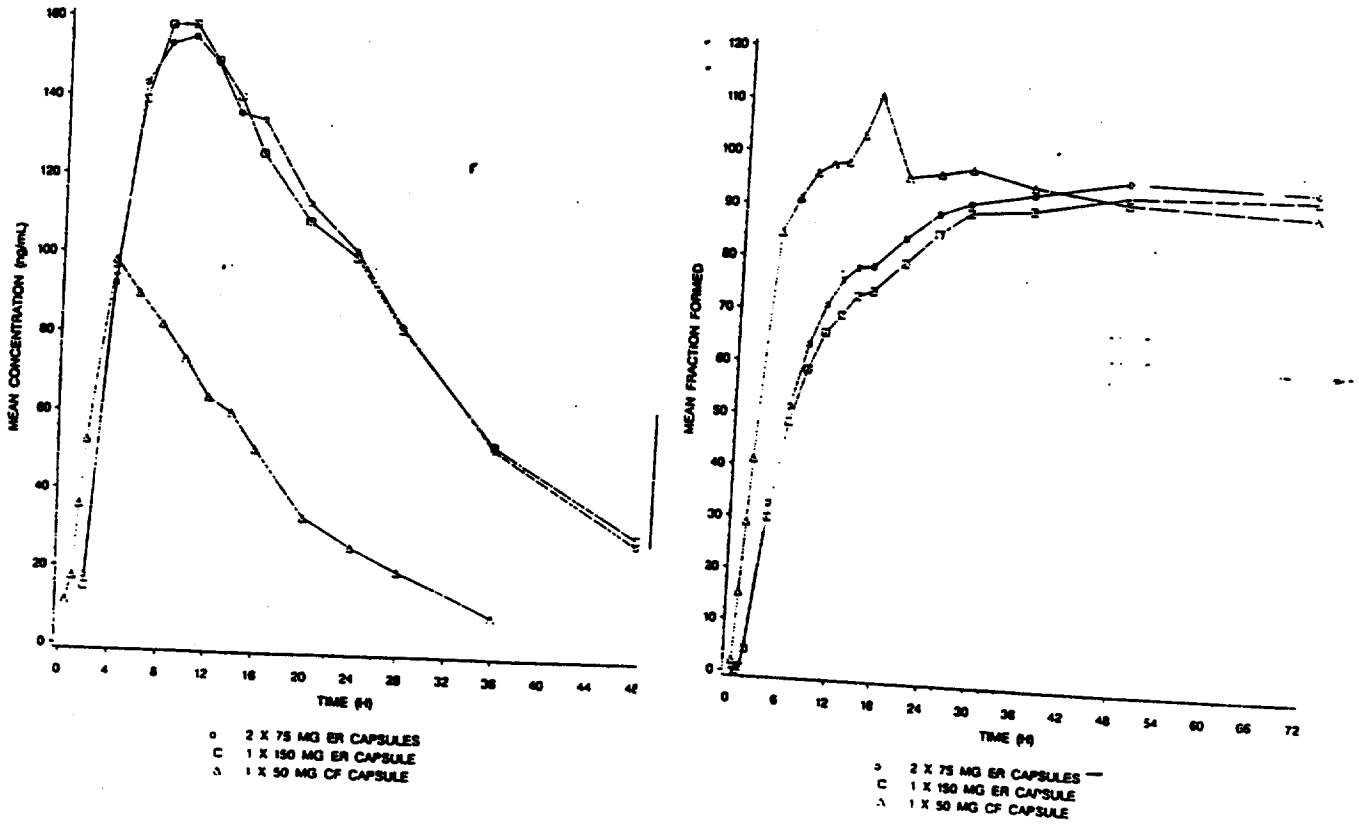
ASSAY PERFORMANCE: Assay conducted at

Assays for venlafaxine and ODV were found to be acceptable.

Mean plasma concentration-time curves and the mean fraction of drug absorbed-time curves of venlafaxine after administration of the 2 venlafaxine ER capsules and the conventional venlafaxine tablet are shown in the following figures.



Mean plasma concentration-time curves and the mean fraction of metabolite formation-time curves of ODV after administration of the 2 venlafaxine ER capsules and the conventional venlafaxine tablet are shown in the following figures.



A summary of venlafaxine PK parameters (mean ± std. dev.) along with 90% confidence intervals, following administration of the three formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	t_{max} (hours)	$t_{1/2}$ (hours)	AUC (ng.hr/ml)	Rel. Bioav - C_{max} (C.I.) Ref: 2x75ER	Rel. Bioav AUC (C.I.)Ref: 2x75ER	Rel. Bioav - C_{max} (C.I.) Ref:50 mg CF	Rel. Bioav AUC (C.I.) Ref:50 mg C
2x75 ER	107 ±42	6.1 ± 1.5	11.8 ± 6.9	1775 ± 1206			42 (38 - 46)	94 (87 - 101)
1x150ER	101 ± 36	5.7 ± 1.5	10.3 ± 4.4	1777 ± 1423	95 (87 - 104)	95 (89 - 103)	40 (36 - 44)	90 (83 - 96)
1x50 CF	82 ± 28	3.0 ± 1.4	5.0 ± 3.2	625 ± 470				

A summary of ODV PK parameters (mean ± std. dev.) along with 90% confidence intervals, following administration of the three formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	t_{max} (hours)	$t_{1/2}$ (hours)	AUC (ng.hr/ml)	Rel. Bioav - C_{max} (C.I.) Ref: 2x75ER	Rel. Bioav AUC (C.I.)Ref: 2x75ER	Rel. Bioav - C_{max} (C.I.) Ref:50 mg CF	Rel. Bioav AUC (C.I.) Ref:50 mg C
2x75 ER	163 ±53	10.5 ± 3.0	13.2 ± 3.3	4516 ± 1523			43 (36 - 51)	88 (84 - 93)
150ER	167 ± 49	12.3 ± 9.2	14.6 ± 4.2	4787 ± 1551	103 (87 - 123)	102 (97 - 108)	45 (37 - 53)	90 (86 - 95)
1x50 CF	120 ± 30	5.5 ± 3.4	9.6 ± 2.5	1758 ± 494				

Since venlafaxine and ODV have similar activity and are equipotent, composite PK parameters can be estimated. A summary of composite (venlafaxine + ODV) AUC (mean ± std. dev.) along with 90% confidence intervals, following administration of the three formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	t_{max} (hours)	AUC (ng.hr/ml)	Rel. Bioav - C_{max} (C.I.) Ref: 2x75ER	Rel. Bioav AUC (C.I.)Ref: 2x75ER	Rel. Bioav - C_{max} (C.I.) Ref:50 mg CF	Rel. Bioav AUC (C.I.) Ref:50 mg CF
2x75 ER	256 ±50	8.2 ± 2.6	6147 ± 1530			48 (45 - 50)	90 (86 - 94)
1x150ER	251 ± 41	7.6 ± 1.3	6425 ± 1444	99 (94 - 104)	101 (97 - 106)	47 (45 - 50)	91 (87 - 96)
1x50 CF	178 ± 36	3.7 ± 1.4	2308 ± 462				

The bioequivalence test criteria were met for C_{max} and AUC of both venlafaxine and ODV between the two venlafaxine ER treatments. The venlafaxine ER formulations produced a lower dose-normalized C_{max} of both venlafaxine and ODV than the conventional formulation, while the dose-normalized AUC met the bioequivalence criteria. No significant differences in pharmacokinetic parameters (except t_{max}) were noted between males and females.

Conclusion: The 150 mg venlafaxine ER capsule (manufactured in Puerto Rico) is bioequivalent to the 75 mg venlafaxine ER capsule (manufactured in NY), the treatment that was used in clinical efficacy and safety trials. In comparison to the approved conventional formulation, the ER formulations provided a lower C_{max} but the same exposure (AUC) after normalization for the administered dose.

STUDY 600-B-136-US: PIVOTAL MULTIPLE DOSE COMPARATIVE BIOAVAILABILITY STUDY

A RELATIVE BIOAVAILABILITY STUDY OF TWO VENLAFAXINE EXTENDED-RELEASE 75 MG FORMULATIONS, ONE VENLAFAXINE EXTENDED RELEASE 150 MG FORMULATION AND THE CONVENTIONAL FORMULATION OF VENLAFAXINE IN HEALTHY ADULT VOLUNTEERS

Reference: Volumes 22, 23 and 24
Investigator:
Study Location:

Objective:

To assess the relative bioavailability of three microsphere encapsulated venlafaxine extended release (ER) formulations, manufactured in NY and PR, administered every 24 hours (q24 hours) for 4 days compared with the venlafaxine conventional formulation (CF) tablet administered every 12 hours (q12 hours) for 4 days.

Study design:

This study is a randomized, open-label, multiple-dose, four period crossover design study preceded by a 3-day dose titration period of venlafaxine conventional formulation 37.5 mg q12 hours, without any washout period between the four periods. 24 healthy adult men and women between 18 and 45 years of age participated in this study. Following a 3-day dose titration period with venlafaxine CF 37.5 mg q12 hours (75 mg/day), each subject received a 4-day treatment (150 mg/day) with the 3 venlafaxine ER formulations (q24 hours) and the venlafaxine CF tablet (75 mg q12 hours) in four separate study periods.

Study drug:
37.5 mg venlafaxine CF tablets (PR), batch # EXP 1324/2GTL, batch size
75 mg venlafaxine CF tablets (PR), batch # EXP 0400/1TBX, batch size
75 mg venlafaxine ER (NY) capsules, batch # 3THV, batch size
75 mg venlafaxine ER (PR) capsules, batch # A94D016/4TBL, batch size
150 mg venlafaxine ER (PR) capsules, batch # A94D018/3TJB, batch size

Subjects reported to the study site the evening before the study day 1. During the dose titration period on study days 1 - 3, each subject received venlafaxine 37.5 mg CF q12 hours. On the morning of study day 4, the subjects began one of the four treatments which they maintained through study day 7. Subsequent treatments were administered on study days 8 - 11, 12 - 15 and 16 - 19. All doses were administered postprandially and with 250 ml of room temperature water.

Blood was collected for determination of plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine on the 3rd day of each dosing regimen at '0' hours, on the 4th day of each dosing regimen at 0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours after the ER treatments

and at 0, 0.5, 1, 2, 4, 6, 8, 12, 12.5, 13, 14, 16, 18, 20 and 24 hours after administration of the morning dose of the CF treatment. Pharmacokinetic analysis of data was performed using model-independent techniques. Analysis was conducted using log transformed data. The pharmacokinetic parameters were compared among the four treatments using an ANOVA. Assessments of the magnitude of difference between the two treatments were made with the two one-sided test procedure applied to log-transformed data. The 75 mg ER formulation manufactured in NY was used as the main reference since this formulation was used in phase II and III clinical trials. The 75 mg CF formulation was used as a general reference for comparison of ER formulations to the currently approved CF formulation.

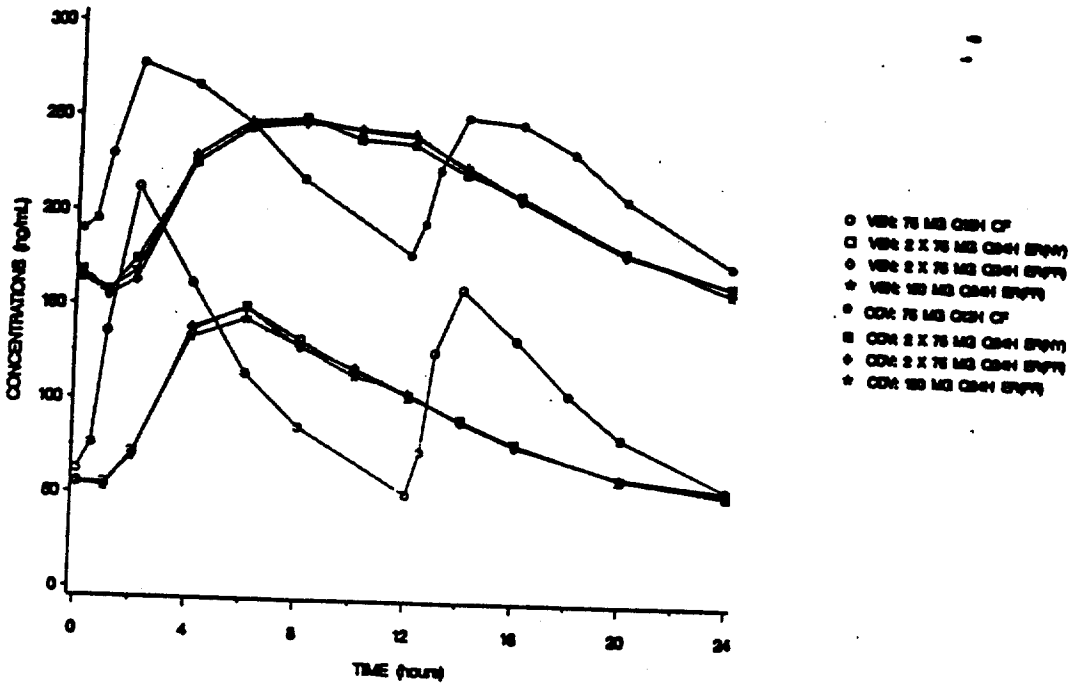
Additional blood and urine samples were also collected at different time points to determine the enantiomeric ratios of venlafaxine and ODV.

Results:

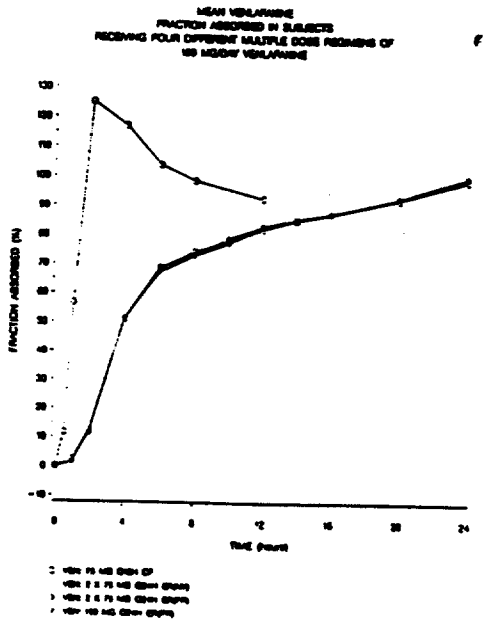
ASSAY PERFORMANCE: Assay conducted at

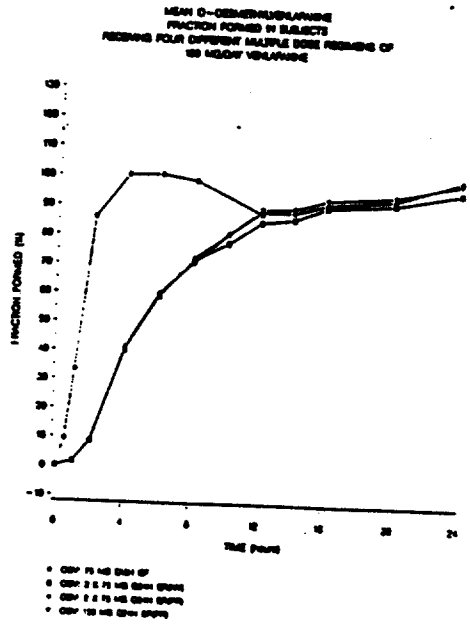
Assays for venlafaxine and ODV were found to be acceptable.

Mean plasma concentration-time curves of venlafaxine and ODV after administration of the 3 venlafaxine ER capsules and the conventional venlafaxine tablet are shown in the following figure.



Mean venlafaxine fraction absorbed-time curves and the mean fraction of metabolite formation-time curves of ODV after administration of the 3 venlafaxine ER capsules and the conventional venlafaxine tablet are shown in the following figures.





A summary of venlafaxine multiple dose PK parameters (mean ± std. dev.) along with 90% confidence intervals, following administration of the four formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{24hrs} (ng.hr/ml)	R_f	Rel. Bioav - C_{max} (C.I.) Ref: 2x75ER (NY)	Rel. Bioav AUC (C.I.)Ref: 2x75ER (NY)	Rel. Bioav - C_{max} (C.I.) Ref:75 mg CF	Rel. Bioav AUC (C.I.) Ref:75 mg C
75 mg CF q12h	228 ± 86	50 ± 35	2604 ± 1325	1.86 ± 0.68	-	-	-	-
2x75 ER NY q24h	155 ± 71	51 ± 37	2246 ± 1216.	1.23 ± 0.34	-	-	66 (61 - 70)	90 (86 - 95)
2x75 ER PR q24h	157 ± 71	50 ± 37	2240 ± 1218	1.27 ± 0.34	101 (94 - 108)	98 (93 - 103)	66 (61 - 70)	89 (85 - 93)
1x150ER PR q24h	149 ± 79	51 ± 44	2222 ± 1403	1.21 ± 0.35	94 (88 - 101)	96 (91 - 101)	62 (58 - 66)	87 (82 - 91)

Confidence intervals for C_{min} using the 75 mg CF as reference are:
2x75 mg ER(NY): 92%(85-100); 2x75 mg ER(PR): 88%(81 - 95); 1x150 mg ER(PR): 86%(79 - 93)

A summary of ODV PK parameters (mean ± std. dev.) along with 90% confidence intervals, following multiple dose administration of the four formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{24hrs} (ng.hr/ml)	R_f	Rel. Bioav - C_{max} (C.I.) Ref: 2x75ER (NY)	Rel. Bioav AUC (C.I.)Ref: 2x75ER (NY)	Rel. Bioav - C_{max} (C.I.) Ref:75 mg CF	Rel. Bioav AUC (C.I.) Ref:75 mg C
75 mg CF q12h	290 ± 117	167 ± 69	5402 ± 2131	0.54 ± 0.20	-	-	-	-
2x75 ER NY q24h	256 ± 108	148 ± 61	5036 ± 2115	0.50 ± 0.14	-	-	97 (93 - 102)	98 (96 - 101)
2x75 ER PR q24h	266 ± 105	144 ± 65	5019 ± 2055	0.57 ± 0.22	104 (99 - 109)	100 (97 - 103)	101 (96 - 106)	98 (96 - 101)
1x150ER PR q24h	260 ± 109	150 ± 62	5052 ± 2087	0.51 ± 0.14	101 (97 - 106)	100 (97 - 103)	98 (94 - 103)	99 (96 - 102)

Confidence intervals for C_{min} using the 75 mg CF as reference are:
2x75 mg ER(NY): 81%(76-86); 2x75 mg ER(PR): 78%(73 - 83); 1x150 mg ER(PR): 81%(76 - 87)

Since venlafaxine and ODV have similar activity and are equipotent, composite PK parameters can be estimated. A summary of composite (venlafaxine + ODV) AUC (mean ± std. dev.) along with 90% confidence intervals, following multiple dose administration of the four formulations are presented in the following table:

Treatment	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{24hr} (ng.hr/ml)	R_f	Rel. Bioav - C_{max} (C.I.) Ref: 2x75ER (NY)	Rel. Bioav AUC (C.I.)Ref: 2x75ER (NY)	Rel. Bioav - C_{max} (C.I.) Ref:75 mg CF	Rel. Bioav AUC (C.I.) Ref:75 mg C
75 mg CF q12h	508 ± 121	217 ± 61	8014 ± 1839	0.89 ± 0.23	-	-	-	-
2x75 ER NY q24h	405 ± 107	200 ± 56	7284 ± 1973	0.68 ± 0.14	-	-	84 (80 - 88)	95 (92 - 97)
2x75 ER PR q24h	413 ± 100	196 ± 60	7260 ± 1801	0.72 ± 0.19	101 (97 - 107)	100 (97 - 103)	85 (81 - 89)	94 (91 - 97)
1x150ER PR q24h	402 ± 109	202 ± 60	7275 ± 1899	0.66 ± 0.14	98 (94 - 103)	100 (97 - 103)	82 (78 - 86)	94 (91 - 97)

Confidence intervals for C_{min} using the 75 mg CF as reference are:
2x75 mg ER(NY): 82%(78-87); 2x75 mg ER(PR): 80%(76 - 85); 1x150 mg ER(PR): 82%(78 - 87)

CONCLUSIONS: When the three ER formulations were compared to the approved CF tablet, the AUC for venlafaxine and ODV (and the composite) were within the confidence interval criteria of 80 - 125%. Fluctuation index for all ER products was separately shown to be less than the fluctuation index for the CF (immediate release) formulation for venlafaxine and the composite, and was comparable for ODV.

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STUDY 600-B-145-US: FOOD EFFECT STUDY ON FINAL 150 MG TO-BE MARKETED CAPSULE

A RANDOMIZED, OPEN-LABEL, CROSSOVER STUDY OF THE EFFECT OF FOOD ON THE PHARMACOKINETICS OF 150 MG VENLAFAXINE EXTENDED-RELEASE CAPSULES (VENLAFAXINE ER) IN HEALTHY ADULT VOLUNTEERS

Reference: Volumes 31 and 32
Investigator: Richard Fruncillo, M.D., Ph.D.
Study Location: Wyeth Ayerst Research, Clinical Pharmacology Unit, Philadelphia, PA

Objective:

To characterize the effect of food on the bioavailability and pharmacokinetic profile of venlafaxine ER following single dose administration of 150 mg venlafaxine ER capsules following a high fat breakfast.

Study design:

This is a randomized, 2-way crossover study of single doses of 150 mg venlafaxine ER capsules taken either with or without food. 16 healthy male volunteers participated in the study (15 completed the entire study). The two assessment periods were separated by a 5 to 7 day washout period.

Study drug: Venlafaxine ER 150 mg capsule (highest strength; Puerto Rico), single dose, batch #A94D018, batch size .

Subjects reported to the study site the afternoon before the dosing day. At about 8 a.m. on day 1, after at least an 8 hour fast (fasting treatment) or within 30 minutes of a standardized high fat breakfast (fed treatment), each subject received 150 mg venlafaxine ER capsule along with 250 ml of water according to one of the 2 treatment sequences shown below:

Sequence 1: Fed treatment, then washout, then fasting treatment.
Sequence 2: Fasting treatment, washout and then fed treatment.

The standardized high fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 pieces of toast with butter, 4 oz of hashbrown potatoes cooked in butter and 8 oz of whole milk.

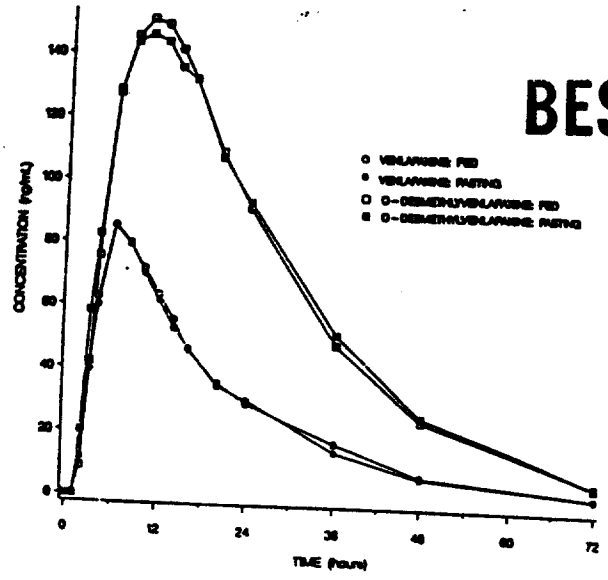
Blood was collected for determination of plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours after each dose. Pharmacokinetic analysis of data was performed using model-independent techniques. $AUC_{0-\infty}$ and C_{max} were log transformed before analysis. These endpoints were analyzed using an ANOVA model allowing for effects of subjects within sequence, sequence, period and treatment as factors in the model to identify any significant treatment differences. Assessment of the magnitude of difference between the two treatments were made with the two one-sided test

procedure applied to log-transformed data. Pharmacodynamic assessments were made using the visual analog scale for nausea.

Results:
ASSAY PERFORMANCE: Assay conducted at

Assays for venlafaxine and ODV were found to be acceptable.

Mean plasma concentration-time curves of venlafaxine and ODV after administration of 150 mg venlafaxine ER capsules under fasted conditions and fed conditions are shown in the following figure.



The mean plasma concentration profiles were similar with and without food, with mean t_{max} occurring at about 6 hours for venlafaxine and 12 hours for ODV after dosing. C_{max} and $AUC_{0-\infty}$ were similar for both formulations.

Results of the pharmacokinetic analysis (on log transformed parameters) are summarized in the following table:

Parameters	Fasted treatment (Reference)	Fed treatment	Geo. Mean Ratio (Fed/Fasted)	90% confidence interval
Venlafaxine				
$AUC_{0-\infty}$, ng.hr/ml	1834 ± 2511	1877 ± 2572	99%	0.92 - 1.07
C_{max}, ng/ml	89 ± 56	90 ± 57	99%	0.91 - 1.07
T_{max}, hours	6.1 ± 0.5	6.5 ± 2.3	102%	---
O-desmethylvenlafaxine (ODV)				
$AUC_{0-\infty}$, ng.hr/ml	4418 ± 1277	4331 ± 1208	99%	0.93 - 1.05
C_{max}, ng/ml	151 ± 58	154 ± 56	103%	1.00 - 1.07
T_{max}, hours	11.5 ± 4.0	12.0 ± 4.0	105%	---

The pharmacokinetic profiles of venlafaxine and ODV were not significantly different between fasted and fed administration of 150 mg venlafaxine ER.

PHARMACODYNAMICS: Single dose administration of 150 mg venlafaxine ER capsule with a high fat meal did not affect the incidence or severity of nausea. In addition, for subjects who experienced nausea, significant variability was exhibited in the plasma concentration vs. nausea relationship and PK/PD modeling did not yield satisfactory results.

Calculation of confidence intervals for $AUC_{0-\infty}$ and C_{max} for venlafaxine and ODV is shown below:

FOOD EFFECT ON 150 MG VENLAFAXINE ER CAPSULE

VENLAFAXINE C_{MAX} FOOD EFFECT

ERROR MEAN SQUARE . . 1.525675E-02
REFERENCE MEAN 4.380901
TEST MEAN 4.371144
NUMBER OF SUBJECTS . . 15

POWER ANALYSIS

POWER FOR .2 M(r)= 95.87354 %
POWER FOR -.2 M(r)= 99.23145 %

DETECTABLE DIFFERENCE: 14.64596 %

DEGREES OF FREEDOM . . 13
NUMBER OF TREATMENTS . 2
DELTA 2

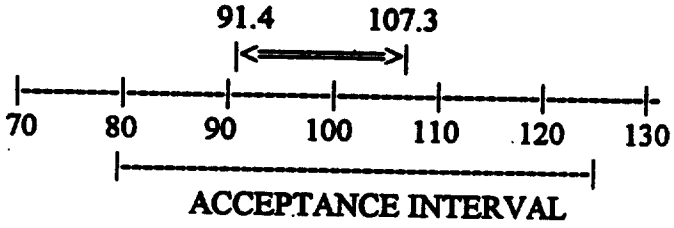
10 SUBJECTS NEEDED FOR A
19.30209 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 91.42702
UPPER CI (% OF REF MEAN): 107.2632
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: 0.00020
p> 120 % REF MEAN: 0.00047
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 91.4% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 107.3% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -0.22% OF THE REFERENCE MEAN.

VENLAFAXINE AUC FOOD EFFECT

ERROR MEAN SQUARE . . 1.379156E-02
REFERENCE MEAN 7.158514
TEST MEAN 7.147079
NUMBER OF SUBJECTS . . 15
DEGREES OF FREEDOM . . 13
NUMBER OF TREATMENTS . 2
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= 97.16402 %
POWER FOR -.2 M(r)= 99.52993 %

DETECTABLE DIFFERENCE: 13.87713 %

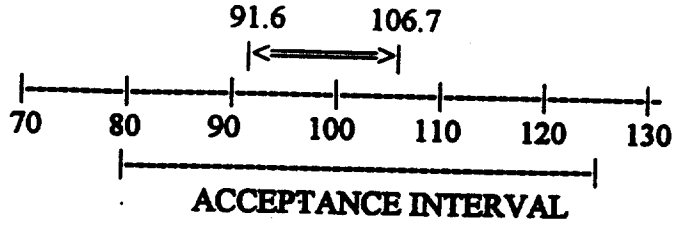
10 SUBJECTS NEEDED FOR A
18.27003 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 91.63334
UPPER CI (% OF REF MEAN): 106.6631
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: 0.00014
p> 120 % REF MEAN: 0.00029
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 91.6% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 106.7% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -0.16% OF THE REFERENCE MEAN.

. *ODV C_{MAX} FOOD EFFECT*

ERROR MEAN SQUARE . . 2.75211E-03
REFERENCE MEAN 4.895256
TEST MEAN 4.928899
NUMBER OF SUBJECTS . . 15
DEGREES OF FREEDOM . . 13
NUMBER OF TREATMENTS . 2
DELTA 2

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 99.97201
UPPER CI (% OF REF MEAN): 106.9901
CONCLUSION: PASS

POWER ANALYSIS

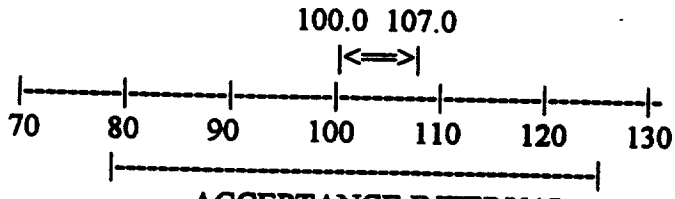
POWER FOR .2 M(r)= > 99.997 %
POWER FOR -.2 M(r)= > 99.997 %

DETECTABLE DIFFERENCE: 5.976796 %

15 SUBJECTS NEEDED FOR A
5.976796 % DETECTABLE DIFFERENCE

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00003
p> 120 % REF MEAN: <0.00003
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 100.0% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 107.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +0.69% OF THE REFERENCE MEAN.

ODV AUC FOOD EFFECT

ERROR MEAN SQUARE .. 8.91954E-03
REFERENCE MEAN 8.3273
TEST MEAN 8.319078
NUMBER OF SUBJECTS .. 15
DEGREES OF FREEDOM .. 13
NUMBER OF TREATMENTS . 2
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= 99.60057 %
POWER FOR -.2 M(r)= 99.95982 %

DETECTABLE DIFFERENCE: 11.01619 %

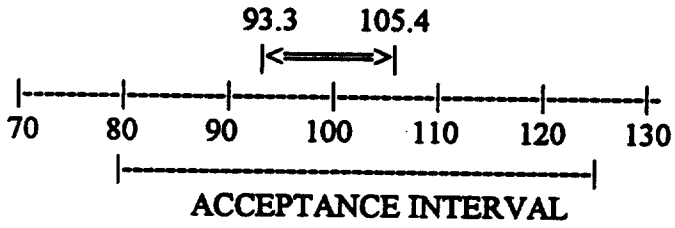
8 SUBJECTS NEEDED FOR A
17.15522 % DETECTABLE DIFFERENCE

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 93.30528
UPPER CI (% OF REF MEAN): 105.427
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: <0.00003
p> 120 % REF MEAN: 0.00005
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 93.3% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 105.4% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -0.10% OF THE REFERENCE MEAN.

Comments:

Food did not significantly affect the pharmacokinetics of venlafaxine and ODV following administration of venlafaxine ER capsule with or without food.

Conclusion: Based on the data provided, there is no food effect on the bioavailability of venlafaxine and ODV following administration of 150 mg venlafaxine ER capsule (final highest strength formulation). Dose dumping did not occur upon administration of venlafaxine ER with high fat meal. Therefore, based on the pharmacokinetic data, patients may take venlafaxine ER with or without meals.

STUDY 600-B-138-US: FOOD EFFECT STUDY ON 75 MG VENLAFAXINE ER CAPSULE

A RANDOMIZED, OPEN-LABEL, CROSSOVER STUDY OF THE EFFECT OF FOOD ON THE PHARMACOKINETICS OF VENLAFAXINE EXTENDED RELEASE CAPSULES (VENLAFAXINE ER) IN HEALTHY MALE VOLUNTEERS

Reference: Volumes 29 and 30
Investigator: Richard Fruncillo, M.D., Ph.D.
Study Location: Wyeth-Ayerst Research, Clinical Pharmacology Unit, Philadelphia, PA
Objective:

To assess the effect of food on the pharmacokinetic profile of venlafaxine and its active metabolite, ODV, following single dose administration of 75 mg venlafaxine ER capsules.

Study design:

This is an open-label, randomized, 2-way crossover study of single dose of 75 mg venlafaxine ER capsules taken either in the fasted or fed state. 12 healthy male volunteers between 18 and 45 years of age participated in the study. The two dosing periods were separated by a 5 to 7 day washout period.

Study drug: Venlafaxine ER 75 mg capsule (clinically studied formulation, manufactured in NY), single oral dose 75 mg, batch #3THV, batch size

Subjects reported to the study site the afternoon before the dosing day. At about 8 a.m. on day 1, after at least an 8 hour fast (fasting treatment) or within 30 minutes of a standardized high fat breakfast (fed treatment), each subject received 75 mg venlafaxine ER capsule along with 250 ml of water according to one of the 2 treatment sequences shown below:

Sequence 1: Fed treatment, then washout, then fasting treatment.
Sequence 2: Fasting treatment, washout and then fed treatment.

The standardized high fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 pieces of toast with butter, 4 oz of hashbrown potatoes cooked in butter and 8 oz of whole milk. The subjects continued to fast until 4 hours after dose administration.

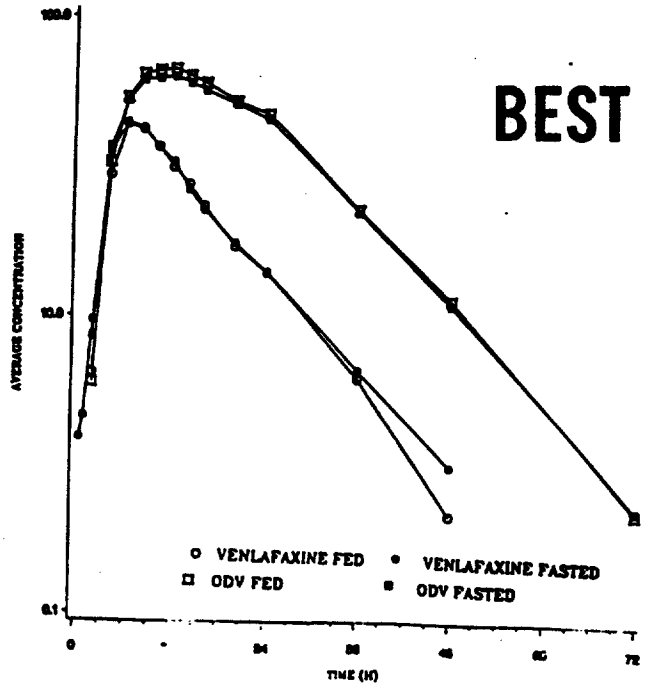
Blood was collected for determination of plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine at 0, 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 20, 24, 36, 48 and 72 hours after drug administration. Plasma concentrations of venlafaxine and its active metabolite, ODV were analyzed using model-independent techniques. $AUC_{0-\infty}$ and C_{max} were log transformed before analysis. These endpoints were analyzed using an ANOVA model allowing for effects of subjects within sequence, sequence, period and treatment as factors in the model to identify any significant treatment differences. Assessment of the magnitude of difference between the two treatments were made with the two one-sided test procedure applied to log-transformed data.

Results:

ASSAY PERFORMANCE: Assay conducted at Bioassay Laboratories, Inc., Houston, TX

Assays for venlafaxine and ODV were found to be acceptable.

Mean plasma concentration-time curves of venlafaxine and ODV after administration of 75 mg venlafaxine ER capsules with or without food are shown in the following figure.



The mean plasma concentration profiles were similar after both fasted and fed administration.

The following table summarizes the pharmacokinetic parameters of venlafaxine and ODV following single dose administration of 75 mg venlafaxine ER capsule under fasted and fed conditions:

Parameters	Fasted treatment (Reference)	Fed treatment	Geo. Mean Ratio (Fed/Fasted)	90% confidence interval
Venlafaxine				
$AUC_{0-\infty}$, ng.hr/ml	841 ± 296	797 ± 248	96%	0.87 - 1.07
C_{max}, ng/ml	45 ± 16	45 ± 14	101%	0.89 - 1.14
T_{max}, hours	6.5 ± 1.2	6.7 ± 1.6	102%	---
O-desmethylvenlafaxine (ODV)				
$AUC_{0-\infty}$, ng.hr/ml	1967 ± 609	1982 ± 565	101%	0.93 - 1.09
C_{max}, ng/ml	65 ± 18	69 ± 18	107%	1.00 - 1.14
T_{max}, hours	10.7 ± 2.2	11.0 ± 2.0	103%	---

The pharmacokinetic profiles of venlafaxine and ODV were not significantly different between fasted and fed administration of 75 mg venlafaxine ER.

Conclusion: Results indicate that there is no food effect on the pharmacokinetics of venlafaxine and ODV when administered as 75 mg venlafaxine ER capsules. Dose dumping does not occur upon administration of venlafaxine ER with high fat meal. Therefore, based on the pharmacokinetic data, patients may take venlafaxine ER with or without meals.

STUDY 600-B-139-US: EFFECT OF AM vs PM ADMINISTRATION

A RANDOMIZED, MULTIPLE DOSE, CROSSOVER STUDY OF THE EFFECT OF AM VERSUS PM DOSE ADMINISTRATION ON THE PHARMACOKINETICS OF VENLAFAXINE EXTENDED RELEASE CAPSULES (VENLAFAXINE ER) IN HEALTHY MALE VOLUNTEERS

Reference: Volumes 33 and 34
Investigator:
Study Location:
Objective:

To determine the effect of diurnal variation on the multiple dose pharmacokinetic profile of venlafaxine ER by administration of a 75 mg venlafaxine ER capsule once a day for 4 days either in the morning (AM) or in the evening (PM).

Study design:

This is an open-label, randomized, 2-way crossover study of multiple doses of 75 mg venlafaxine ER capsules qd taken either in the AM or in the PM for 4 days each. 18 healthy male volunteers between 18 and 45 years of age participated in the study. The two dosing periods were separated by 36 hours.

Study drug: Venlafaxine ER 75 mg capsule, multiple dose 75 mg qd for 4 days, batch #3THV, batch size

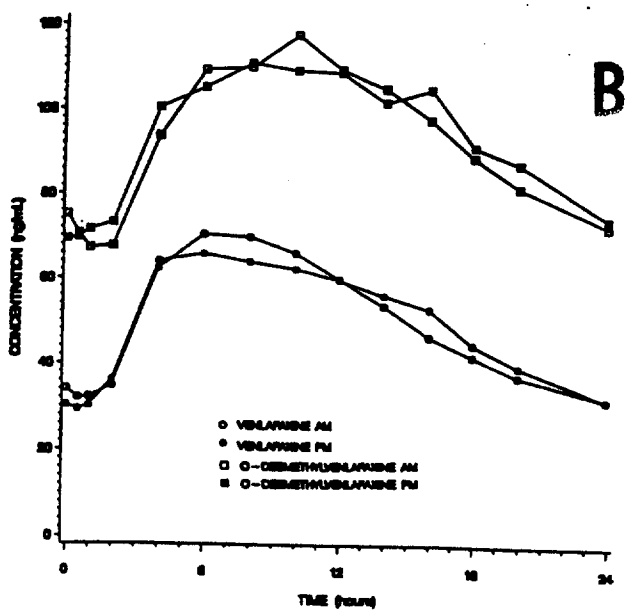
Subjects reported to the study site the afternoon before the dosing day. On each dosing day, each subject received a single 75 mg venlafaxine capsule along with 250 ml of water soon after a standardized meal (i.e. breakfast for AM administration and dinner for PM administration). For the AM treatment, the dosing occurred at about 6 a.m. on days 1 to 4 for subjects in sequence 1 and on days 6 to 9 for sequence 2. For the PM treatment, dosing occurred at about 6 p.m. on days 1 to 4 for sequence 2 and on days 5 to 8 for sequence 1.

Blood was collected for determination of plasma concentrations of venlafaxine and its active metabolite, O-desmethylvenlafaxine at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, and 36 hours after administration of the last venlafaxine ER dose of each study period. Plasma concentrations of venlafaxine and its active metabolite, ODV were analyzed using model-independent techniques. AUC_{0-} and C_{max} were log transformed before analysis. These endpoints were analyzed using an ANOVA model allowing for effects of subjects within sequence, sequence, period and treatment as factors in the model to identify any significant treatment differences. Assessment of the magnitude of difference between the two treatments were made with the two one-sided test procedure applied to log-transformed data.

Results:
ASSAY PERFORMANCE: Assay conducted at

Assays for venlafaxine and ODV were found to be acceptable.

Mean plasma concentration-time curves of venlafaxine and ODV after administration of 75 mg venlafaxine ER capsules once daily for 4 days either in AM or PM are shown in the following figure.



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The mean plasma concentration profiles were similar after both AM and PM administration.

The following table summarizes the multiple-dose pharmacokinetic parameters of venlafaxine and ODV for the AM and PM treatments:

Parameters	AM treatment (Reference)	PM treatment	Geo. Mean Ratio (PM/AM)	90% confidence interval
Venlafaxine				
AUC_{0-24}, ng.hr/ml	1220 ± 1039	1222 ± 990	104%	0.99 - 1.10
C_{max}, ng/ml	75 ± 52	72 ± 49	97%	0.91 - 1.04
T_{max}, hours	7.2 ± 2.2	6.3 ± 2.9	85%	---
R_f	1.17 ± 0.41	1.09 ± 0.36	94%	0.88 - 1.01
O-desmethylvenlafaxine (ODV)				
AUC_{0-24}, ng.hr/ml	2251 ± 963	2281 ± 995	100%	0.96 - 1.05
C_{max}, ng/ml	121 ± 53	117 ± 52	96%	0.91 - 1.02
T_{max}, hours	9.9 ± 2.8	10.4 ± 4.0	101%	---
R_f	0.59 ± 0.16	0.55 ± 0.12	96%	0.88 - 1.04

The pharmacokinetic profiles of venlafaxine and ODV were not significantly different between AM and PM administration of 75 mg venlafaxine ER once a day.

Comments:

Based on a pharmacokinetic study with the conventional formulation of venlafaxine, it was concluded previously that there was no diurnal variation in pharmacokinetics of venlafaxine and ODV following multiple oral doses of 50 mg q8hours. This means that the disposition of venlafaxine and ODV does not exhibit diurnal variation. Therefore, the current study was conducted to assess the effect of time of administration (AM vs. PM) on only the absorption profile of venlafaxine from venlafaxine ER.

Conclusion: Results indicate that there is no diurnal variation in pharmacokinetics of venlafaxine administered as venlafaxine ER capsules. Therefore, patients who are being treated with venlafaxine ER may take their daily dose of venlafaxine ER either in the morning or evening, provided that they take it at approximately the same time each day.

STUDY 600-A-131-US: PK OF VENLAFAXINE IN EXTENSIVE AND POOR METABOLIZERS

AN OPEN-LABEL STUDY OF PHARMACOKINETICS OF VENLAFAXINE IN EXTENSIVE AND POOR METABOLIZERS OF DEXTROMETHORPHAN

Reference: Volumes 41, 42, 43, 44 and 45

Investigator:

Study Location:

2) Wyeth-Ayerst Clinical Pharmacology Unit, Graduate Hospital, Philadelphia, PA

Objective:

To determine the effect of CYP2D6 genetic polymorphism on the pharmacokinetic profile of venlafaxine and its metabolites after single and multiple doses of venlafaxine.

Study design:

This is an open-label, parallel group, single and multiple design study consisting of doses of 37.5 mg and 75 mg BID venlafaxine IR tablets. 15 healthy male volunteers between 18 and 45 years of age participated in the study. This study is conducted in healthy volunteers who were phenotyped. Dextromethorphan phenotyping was performed by determining the metabolic ratio of dextromethorphan to dextrorphan in urine. For this purpose, 60 mg of dextromethorphan was orally administered and urine collected for at least 8 hours after drug administration. Subjects with a metabolic ratio ≤ 0.30 were classified as CYP2D6 extensive metabolizers and those with >0.30 were classified as CYP2D6 poor metabolizers.

Study drug:

1) 37.5 mg Venlafaxine tablets, multiple dose 37.5 mg bid for 5 days, batch #EXP1324 (2TCC), batch size

2) 75 mg Venlafaxine tablets, multiple dose 75 mg bid for 5 days, batch #EXP0400 (1TBX), batch size

Subjects reported to the study site the afternoon before the dosing day. On each dosing day (days 1 - 10), each subject received the scheduled treatment dose soon after a standardized meal. All subjects received 37.5 mg venlafaxine IR tablets BID from days 1 to 5 and then 75 mg BID on days 5 to 10.

Blood was collected for determination of plasma concentrations of venlafaxine (S, R and racemate) and its metabolites, O-desmethylvenlafaxine (S, R and racemate), N-desmethylvenlafaxine (racemate), and N,O-didesmethylvenlafaxine (racemate) at 0, 0.5, 1, 2, 4, 6, 9 and 12 hours on days 1 and 5 after the AM dose and at 0, 0.5, 1, 2, 4, 6, 9, 12, 24, 48, and 72 hours after the AM dose on day 10. Additional samples were collected pre-dose on days 3, 4, 8 and 9. Urine samples were collected to analyze the same components in urine at 0 - 12 hours after the AM dose on days 1, 5 and 10. Urine was also collected from 12 - 24 hours and 24 - 72 hours on day 10. Plasma concentrations of all the components were analyzed using model-independent techniques. The pharmacokinetic parameters of each analyte were compared between the poor and extensive metabolizer groups at

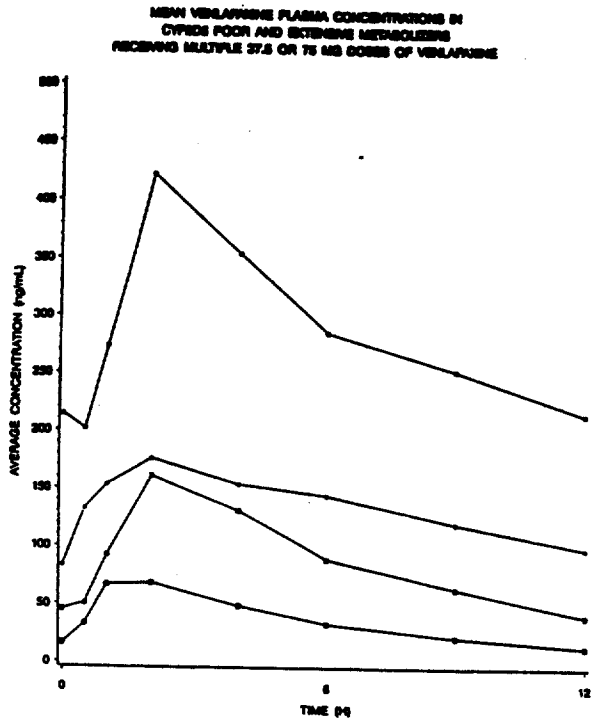
each dose level by using an analysis of variance.

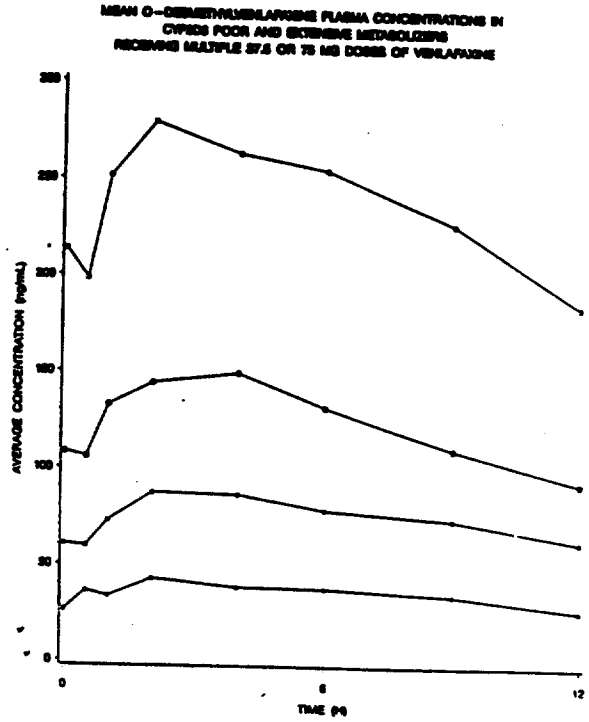
Results:.

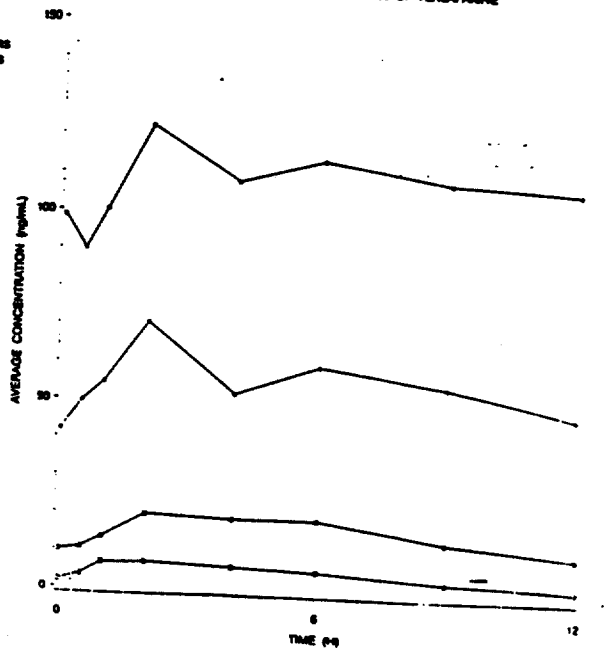
ASSAY PERFORMANCE: Assay conducted at

Assays for venlafaxine (total and individual enantiomers) and its metabolites were found to be acceptable.

Mean plasma concentration-time curves of venlafaxine, ODV, and NDV after administration of multiple doses of 37.5 or 75 mg venlafaxine tablets to CYP2D6 extensive and poor metabolizers are shown in the following three figures.







The following table summarizes the mean ± st. dev for venlafaxine single and multiple dose PK parameters for the extensive (EM) and poor metabolizer (PM) groups:

Treatment	Group (n)	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC* (ng.hr/ml)	Cl/F (L/hr/kg)	Total A_e (%)
37.5 mg	EM (9)	56 ± 17	2.4 ± 0.9	-	370 ± 147	1.65 ± 0.96	-
	PM (6)	118 ± 21	1.2 ± 0.7	-	1455 ± 541	0.38 ± 0.13	-
37.5 mg q12 hrs	EM (9)	80 ± 32	1.7 ± 1.0	14 ± 7	441 ± 148	1.26 ± 0.46	8.5 ± 3.1
	PM (6)	204 ± 62	2.9 ± 2.1	80 ± 49	1645 ± 824	0.36 ± 0.14	26.1 ± 19.3
75 mg q12 hrs	EM (8)	165 ± 56	2.1 ± 0.8	40 ± 21	1082 ± 455	1.18 ± 0.77	9.4 ± 4.1
	PM (6)	431 ± 192	2.3 ± 0.8	193 ± 132	3487 ± 2082	0.36 ± 0.17	28.0 ± 16.4

**AUC is $AUC_{0-\infty}$ for single dose data and AUC_{0-12} for multiple dose data*

The enantiomeric ratio (S/R) of venlafaxine remained almost constant throughout the sampling time period (ratio was 60:40 in most subjects).

The following table summarizes the mean ± stdev for O-desmethylvenlafaxine single and multiple dose PK parameters for the extensive (EM) and poor metabolizer (PM) groups:

Treatment	Group (n)	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC* (ng.hr/ml)	Cl/F (L/hr/kg)	Total A_e (%)
37.5 mg	EM (9)	75 ± 24	5.6 ± 3.8	-	1058 ± 678	0.66 ± 0.38	-
	PM (6)	17 ± 11	6.2 ± 4.4	-	269 ± 350	2.83 ± 1.77	-
37.5 mg q12 hrs	EM (9)	159 ± 34	3.4 ± 1.8	89 ± 32	1493 ± 391	0.35 ± 0.09	50.3 ± 9.2
	PM (6)	44 ± 29	3.6 ± 2.2	24 ± 18	430 ± 295	1.13 ± 0.43	15.9 ± 12.5
75 mg q12 hrs	EM (8)	306 ± 93	4.3 ± 2.7	167 ± 53	2876 ± 838	0.38 ± 0.12	48.9 ± 8.6
	PM (6)	93 ± 64	2.5 ± 1.2	54 ± 41	915 ± 664	1.09 ± 0.42	13.5 ± 11.1

**AUC is $AUC_{0-\infty}$ for single dose data and AUC_{0-12} for multiple dose data*

The following table summarizes the mean ± stdev for N-desmethylvenlafaxine single and multiple dose PK parameters for the extensive (EM) and poor metabolizer (PM) groups:

Treatment	Group (n)	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC* (ng.hr/ml)	Cl/F (L/hr/kg)	Total A_e (%)
37.5 mg	EM (9)	3.6 ± 4.1	4.4 ± 1.7	-	21 ± 22	58 ± 68	-
	PM (6)	16.4 ± 8.4	9.5 ± 1.2	-	150 ± 88	7.0 ± 9.5	-
37.5 mg q12 hrs	EM (9)	8.0 ± 4.4	1.8 ± 1.0	2.3 ± 3.5	57 ± 46	9.09 ± 5.46	1.4 ± 1.1
	PM (6)	80.3 ± 30.4	3.4 ± 2.3	39 ± 16	667 ± 226	0.80 ± 0.23	10.2 ± 2.8
75 mg q12 hrs	EM (8)	23.2 ± 12.4	3.1 ± 1.6	9.4 ± 7.3	190 ± 113	10.8 ± 13.8	1.8 ± 1.3
	PM (6)	126 ± 52	3.3 ± 2.1	85 ± 36	1319 ± 587	0.86 ± 0.33	10.0 ± 4.4

**AUC is $AUC_{0-\infty}$ for single dose data and AUC_{0-12} for multiple dose data*

The following table summarizes the mean ± stdev for composite (venlafaxine and ODV) single and multiple dose PK parameters for the extensive (EM) and poor metabolizer (PM) groups:

Treatment	Group (n)	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC* (ng.hr/ml)	R_f	Total A_e (%)
37.5 mg	EM (9)	124 ± 26	-	1411 ± 603	-	-
	PM (6)	125 ± 23	-	1303 ± 549	-	-
37.5 mg q12 hrs	EM (9)	224 ± 40	105 ± 32	1939 ± 418	0.76 ± 0.16	58.8 ± 9.3
	PM (6)	236 ± 78	91 ± 26	1857 ± 504	0.93 ± 0.28	42.0 ± 15.4
75 mg q12 hrs	EM (8)	449 ± 91	211 ± 62	3963 ± 966	0.74 ± 0.17	58.4 ± 8.8
	PM (6)	518 ± 195	251 ± 119	4405 ± 1876	0.76 ± 0.17	41.5 ± 16.1

**AUC is $AUC_{0-\infty}$ for single dose data and AUC_{0-12} for multiple dose data*

The following table summarizes the mean ± stdev steady state urinary recovery of the unconjugated and total forms of venlafaxine and its 3 metabolites after venlafaxine dose of 75 mg q12 hours:

Compound	Unconjugated A_e (%)		Total A_e (%)	
	EM	PM	EM	PM
Venlafaxine	9 ± 3	27 ± 15	9 ± 4	28 ± 16
ODV	32 ± 6	9 ± 7	49 ± 9	14 ± 11
NDV	2 ± 1	9 ± 4	2 ± 1	10 ± 4

Conclusions:

Results indicate that the formation of ODV (catalyzed by CYP2D6) was significantly lower in CYP2D6 poor metabolizers than the extensive metabolizers. However, the formation of NDV was higher in the CYP2D6 poor metabolizers. This pathway may be partially compensating for the lower CYP2D6-mediated metabolism. Despite the metabolic differences observed between extensive and poor metabolizers, the total exposure to venlafaxine (sum of the two active species, venlafaxine and ODV) was similar for the two groups. Hence, from a pharmacokinetic point of view, both extensive and poor metabolizer groups can be treated with the same dosage regimen of venlafaxine.

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STUDY 600-A-129-US: DRUG INTERACTION STUDY OF VENLAFAXINE AND IMIPRAMINE

AN OPEN-LABEL STUDY OF THE EFFECT OF VENLAFAXINE ON IMIPRAMINE METABOLISM MEDIATED BY THE CYTOCHROME P-450 ISOENZYME CYP2D6 IN EXTENSIVE METABOLIZERS OF DEXTROMETHORPHAN AND MEPHENYTOIN

Reference: Volumes 35, 36, 37, 38 and 39
Investigator:
Study Location:
Objective:

1. To evaluate the effect of venlafaxine on the metabolism of imipramine and its metabolites governed by the cytochrome P-450 isoenzyme CYP2D6.
2. To evaluate the effect of imipramine on the metabolism of venlafaxine and metabolites.

Study design:

This is an open-label, multiple dose, randomized, two parallel-group design study. Eligible subjects were assigned to either group 'A' or 'B'. 27 healthy male volunteers between 18 and 45 years of age participated in the study (26 completed the study). This study is conducted in healthy volunteers who were phenotyped. Dextromethorphan phenotyping was performed by determining the metabolic ratio of dextromethorphan to dextrorphan in urine. Extensive metabolizers of dextromethorphan and mephenytoin were selected.

Study drug, dose and mode of administration:

Group A: Imipramine (oral): days 1 - 14, 50 mg q12h; day 15, 50 mg AM, 25 mg PM; days 16 - 18, 25 mg q12h.
Venlafaxine (oral): days 6 - 10, 37.5 mg q12h; days 11 - 14, 75 mg q12h; day 15, 75 mg AM, 37.5 mg PM; days 16 - 18, 37.5 mg q12h.
Group B: Venlafaxine (oral): days 1 - 14, 37.5 mg q12h; day 15, 37.5 mg AM.
Imipramine (oral): days 6 - 10, 25 mg q12h; days 11 - 14, 50 mg q12h; day 15, 50 mg AM, 25 mg PM; days 16 - 18, 25 mg q12h.

See next page for dosing schedule

Reference therapy:
Group A: Imipramine (50 mg q12 hours) monotherapy on study day 5.
Group B: Venlafaxine (37.5 mg q12 hours) monotherapy on study day 5.

Batch #: Venlafaxine 37.5 mg tablets, PR, lot #1324, batch 2TGL
Imipramine 25 mg tablets, Abbott Lot # 53-282-AF22

Subjects reported to the study site the evening before the dosing day 1. On each dosing day each subject received the scheduled treatment dose soon after a standardized meal. Dosing to subjects in groups A and B was conducted as per the dosing schedule shown above.

SCHEDULED DOSES (TABLETS) OF VENLAFAXINE (mg) AND IMIPRAMINE (mg)

TREATMENT GROUP Drug	Study Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
GROUP A																		
Venlafaxine																		
AM	--	--	--	--	--	37.5	37.5	37.5	37.5	37.5	75	75	75	75	75	37.5	37.5	37.5
PM	--	--	--	--	--	37.5	37.5	37.5	37.5	37.5	75	75	75	75	37.5	37.5	37.5	37.5
Imipramine																		
AM	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	25	25	25
PM	50	50	50	50	50	50	50	50	50	50	50	50	50	50	25	25	25	25
GROUP B																		
Venlafaxine																		
AM	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	--	--	--
PM	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	--	--	--	--
Imipramine																		
AM	--	--	--	--	--	25	25	25	25	25	50	50	50	50	50	25	25	25
PM	--	--	--	--	--	25	25	25	25	25	50	50	50	50	25	25	25	25

Blood was collected before the morning dose on days 1, 4, 5, 6, 9, 10, 11, 14 and 15 and at 0.5, 1, 2, 4, 6, 8, 10 and 12 hours after the morning dose on days 5, 10 and 15. Plasma samples for group A were analyzed for concentrations of imipramine, 2-OH-imipramine, desipramine and 2-OH-desipramine. Plasma samples from group B were analyzed for concentrations of venlafaxine, ODV, NDV and NODV. Urine samples were collected to analyze the same components in urine at -2 to 2 hours and from 0 - 12 hours after the AM dose on days 1, 4, 5, 9, 10, 14 and 15.

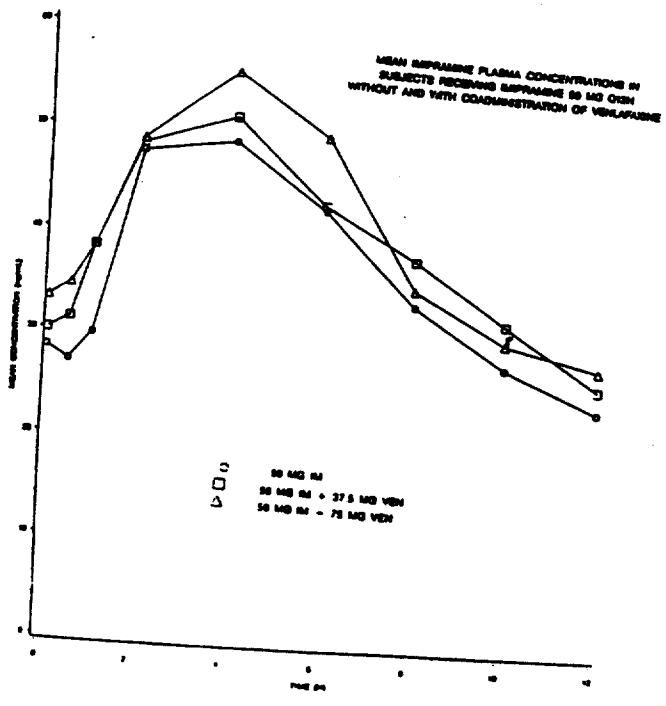
Model-independent methods were used to estimate the pharmacokinetic parameters of venlafaxine and three of its metabolites, ODV, NDV and NODV, as well as imipramine and three of its metabolites, 2-OH-imipramine, desipramine and 2-OH-desipramine. The PK parameters of imipramine and its metabolites with and without coadministration of venlafaxine were compared by using a 2-factor ANOVA and the two one-sided bioequivalence procedure for log-transformed data was applied to C_{max} and AUC to evaluate the observed differences. The same analysis was also performed on the PK parameters of venlafaxine and its metabolites with and without coadministration of imipramine.

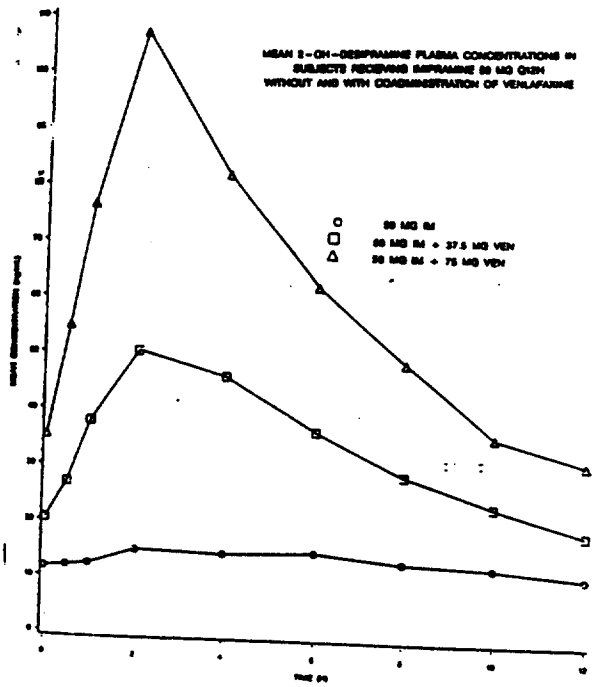
Results:

ASSAY PERFORMANCE: Assay conducted at

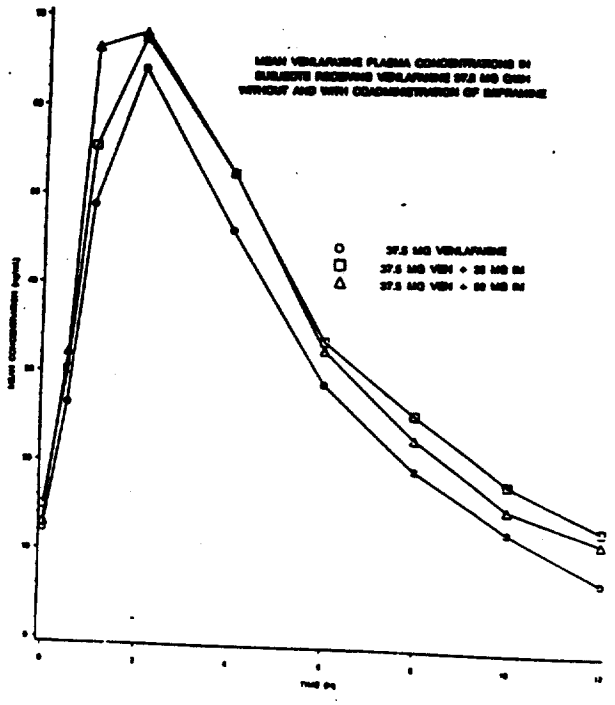
Assays for venlafaxine, its metabolites and imipramine and its metabolites in plasma and urine were found to be acceptable.

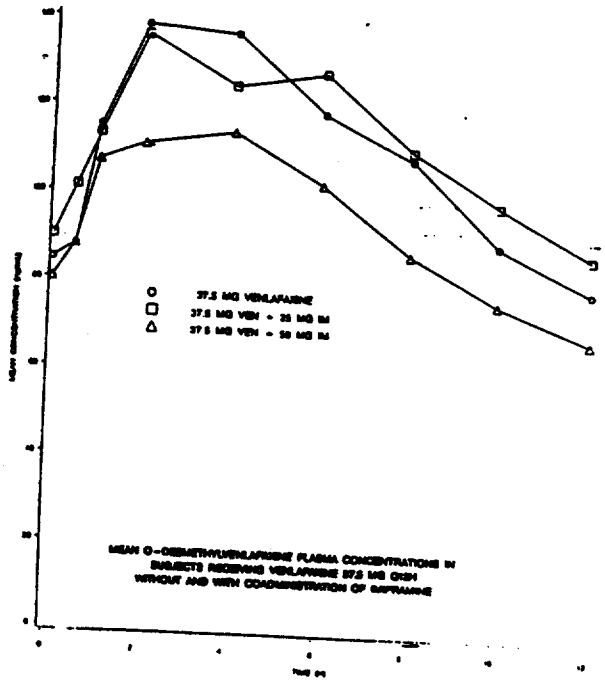
Mean plasma concentration-time curves of imipramine and 2-OH-desipramine after administration of multiple doses of 50 mg q12h of imipramine with and without coadministration of venlafaxine are shown in the following two figures:





Mean plasma concentration-time curves of venlafaxine and ODV after administration of multiple doses of 37.5 mg q12h of venlafaxine with and without coadministration of imipramine are shown in the following two figures:





The following table summarizes the mean ± st. dev for imipramine pharmacokinetic parameters with and without coadministration of venlafaxine:

Treatment	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC (ng.hr/ml)	Cl/F (L/hr/kg)	Total A_e (%)	Cl_r (ml/hr/kg)
Imipramine 50 mg q12h	52 ± 17	3.1 ± 1.3	24 ± 10	438 ± 160	1.77 ± 0.87	0.4 ± 0.6	4 ± 7
Imipramine 50mgq12h + venlafaxine 37.5mg q12h	57 ± 24	3.7 ± 1.8	25 ± 10	477 ± 186	1.64 ± 0.80	0.7 ± 0.7	8 ± 8
Imipramine 50mgq12h + venlafaxine 75 mg q12h	57 ± 24	3.8 ± 1.7	26 ± 15	486 ± 221	1.72 ± 0.89	0.8 ± 0.6	10 ± 8
Bioequivalence tests (%) - Reference is imipramine alone treatment							
Imipramine 50mgq12h + venlafaxine 37.5mg q12h	106 (96-117)	-	106 (94-120)	107 (100-115)	-	-	-
Imipramine 50mgq12h + venlafaxine 75 mg q12h	105 (94-117)	-	104 (91-119)	107 (98-116)	-	-	-

The following table summarizes the mean ± st. dev for desipramine pharmacokinetic parameters with and without coadministration of venlafaxine:

Treatment	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC (ng.hr/ml)	Total A_e (%)	Cl_r (ml/hr/kg)
Imipramine 50 mg q12h	28 ± 14	5.7 ± 2.3	18 ± 10	279 ± 138	1.3 ± 1.0	28± 17
Imipramine 50mgq12h + venlafaxine 37.5mg q12h	39 ± 24	3.3 ± 2.5	22 ± 13	360 ± 189	1.8 ± 1.1	33 ± 27
Imipramine 50mgq12h + venlafaxine 75 mg q12h	41 ± 14	3.5 ± 2.3	25 ± 12	383 ± 150	2.2 ± 1.2	35 ± 13
Bioequivalence tests (%) - Reference is imipramine alone treatment						
Imipramine 50mgq12h + venlafaxine 37.5mg q12h	130 (115-147)	-	116 (102-133)	126 (116-136)	-	-
Imipramine 50mgq12h + venlafaxine 75 mg q12h	158 (138-181)	-	142 (123-165)	143 (131-157)	-	-

The following table summarizes the mean ± st. dev for 2-OH-desipramine pharmacokinetic parameters with and without coadministration of venlafaxine:

Treatment	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC (ng.hr/ml)	Total A_e (%)	Cl_r (ml/hr/kg)
Imipramine 50 mg q12h	16 ± 4	4.5 ± 2.7	10 ± 3	164 ± 43	26.2 ± 9.8	236 ± 110
Imipramine 50mgq12h + venlafaxine 37.5mg q12h	56 ± 13	2.9 ± 1.5	17 ± 5	411 ± 72	29.2 ± 9.8	126 ± 66
Imipramine 50mgq12h + venlafaxine 75 mg q12h	112 ± 36	2.0 ± 0.9	30 ± 10	752 ± 193	28.9 ± 10.0	79 ± 52
Bioequivalence tests (%) - Reference is imipramine alone treatment						
Imipramine 50mgq12h + venlafaxine 37.5mg q12h	353 (301-416)	-	170 (148-195)	253 (221-289)	-	-
Imipramine 50mgq12h + venlafaxine 75 mg q12h	662 (553-792)	-	282 (241-328)	438 (378-508)	-	-

The following table summarizes the mean ± st. dev for venlafaxine pharmacokinetic parameters with and without coadministration of imipramine:

Treatment	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC (ng.hr/ml)	Cl/F (L/hr/kg)	Total A_e (%)	Cl_r (ml/hr/kg)
Venlafaxine 37.5mg q12h	70 ± 24	2.1 ± 1.0	7.7 ± 6.1	368 ± 129	1.58 ± 0.56	5.3 ± 3.3	78 ± 39
Venlafaxine37.5mgq12h+ imipramine 25mg q12h	75 ± 24	2.0 ± 0.7	12.6 ± 7.0	433 ± 136	1.39 ± 0.59	5.6 ± 3.1	61 ± 29
Venlafaxine37.5mgq12h+ imipramine 50mg q12h	80 ± 35	2.1 ± 1.0	9.5 ± 8.9	427 ± 178	1.51 ± 0.77	9.2 ± 4.6	112 ± 75
Bioequivalence tests (%) - Reference is venlafaxine alone treatment							
Venlafaxine37.5mgq12h+ imipramine 25mg q12h	101 (82-126)	-	138 (115-165)	111 (107-130)	-	-	-
Venlafaxine37.5mgq12h+ imipramine 50mg q12h	103 (83-128)	-	120 (96-150)	105 (90-123)	-	-	-

The following table summarizes the mean ± st. dev for ODV pharmacokinetic parameters with and without coadministration of imipramine:

Treatment	C_{max} (ng/ml)	t_{max} (hrs)	C_{min} (ng/ml)	AUC (ng.hr/ml)	Total A_e (%)	Cl_r (ml/hr/kg)
Venlafaxine 37.5mg q12h	147 ± 34	2.8 ± 1.5	74 ± 22	1336 ± 318	51.6 ± 21.3	144 ± 60
Venlafaxine37.5mgq12h+ imipramine 25mg q12h	144 ± 44	3.1 ± 2.0	81 ± 32	1364 ± 441	45.1 ± 25.7	118 ± 54
Venlafaxine37.5mgq12h+ imipramine 50mg q12h	129 ± 51	3.5 ± 3.3	62 ± 28	1131 ± 445	34.9 ± 15.0	153 ± 104
Bioequivalence tests (%) - Reference is venlafaxine alone treatment						
Venlafaxine37.5mgq12h+ imipramine 25mg q12h	95 (83-110)	-	103 (90-118)	99 (87-111)	-	-
Venlafaxine37.5mgq12h+ imipramine 50mg q12h	81 (71-93)	-	76 (67-88)	78 (69-89)	-	-

CONCLUSIONS:

EFFECT OF VENLAFAXINE ON IMIPRAMINE: Venlafaxine did not affect the pharmacokinetics of imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in presence of venlafaxine. The 2-OH desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h).

EFFECT OF IMIPRAMINE ON VENLAFAXINE: Imipramine does not affect the pharmacokinetics of venlafaxine and ODV.

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DISSOLUTION:

A. DISSOLUTION TESTING METHOD DEVELOPMENT:

During the development of dissolution method for venlafaxine ER capsules, the sponsor investigated the effect of dissolution medium, method and agitation speed on dissolution rate of venlafaxine. Water, gastric fluid without enzymes and intestinal fluid without enzymes were tested. Both USP apparatus I (basket) and apparatus II (paddle) were used at agitation speeds of 50, 75 and 100 rpm. Using the above conditions, dissolution samples were collected at 2, 4, 8, 12, 18 and 24 hours and analyzed. The dissolution samples were assayed for venlafaxine by pH of the medium was determined at the beginning and end of the dissolution run where water was the dissolution medium using to determine the effect of the dissolution of venlafaxine on the media.

Such investigation was conducted using at least 3 production size batches for each strength of 75, 100 and 150 mg. This data that has been submitted indicates that the release of venlafaxine from venlafaxine ER capsules is independent of pH (medium), apparatus I or II and rotational speed. The sponsor has selected in water as the final dissolution testing conditions. For illustration purposes in this review, the data from the biobatch, highest strength (150 mg ER capsules, batch # 386549A (A94D018)) has been presented.

Figures on next page show the dissolution profiles generated on 150 mg ER capsules using different testing conditions.

CONCLUSION: Results indicate that the dissolution of venlafaxine from venlafaxine ER capsules is independent of testing apparatus I or II and agitation speed. Although dissolution in gastric fluid is slightly lower compared to the other media tested, the difference is very minimal. Hence, the dissolution of venlafaxine is almost independent of pH of medium as well. **The final testing conditions selected by the sponsor are:** This method is acceptable to OCPB.

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C. DISSOLUTION SPECIFICATIONS:

SPONSOR SELECTED DISSOLUTION SPECIFICATIONS:

Using the correlation developed above, plasma concentration-time profiles of venlafaxine were predicted for the dissolution profiles obtained with the lower and upper dissolution specifications suggested by the sponsor. The method for prediction was exactly the same as described above under evaluation.

SPONSOR'S
DISSOLUTION SPECIFICATIONS:

The sponsor suggested dissolution specifications range will result in a width of 28% on C_{max} and 27.5% on AUC. Hence, in order to reduce this width on C_{max} and AUC, the agency recommends the following specifications.

Predictions based on FDA SELECTED DISSOLUTION SPECIFICATIONS:
2 HR ( ); 4 HR ( ); 8 HR ( ); 12 HR ( ); 20 HR (nlt)
150 mg Effexor XR capsule

C_{max}
Predicted =
Observed (TARGET) = 94.4 ng/ml
Width of predictions (between lower and upper specs): 24.8%

T_{max}
Predicted =
Observed = 6 hours

AUC_{0-24}
Predicted =
Observed (TARGET) = 1230.2 ng.hr/ml
Width of predictions (between lower and upper specs): 24%

1. These recommended specifications result in C_{max} and AUC range of about 24%, which although narrower than the sponsor-selected specification (of 28% range), still result in a width of >20%. However, this FDA selected specification should be allowed since the dissolution specifications that will generate a C_{max} and AUC range of 20% will be quite restrictive.
2. The sponsor has selected the last dissolution specification time point at 24 hours. Although, the predictability is quite similar whether the last specification is at 20 or 24 hours, it is our recommendation that the last time point for specification be set very soon after of drug is dissolved. It is meaningless to have a specification at a time point much beyond that for QC purposes.

CONCLUSION:
The agency recommended dissolution specifications for the four strengths of Effexor XR capsules are as follows:

TIME	% DISSOLVED
2 HR	
4 HR	
8 HR	
12 HR	
20 HR	

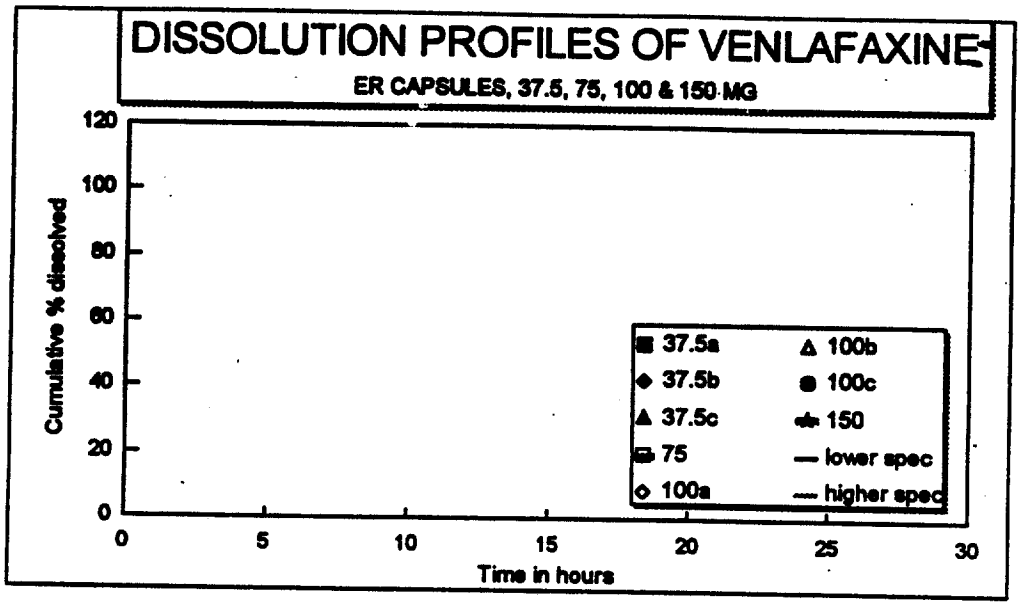
D. WAIVER FOR 37.5 AND 100 MG STRENGTHS THAT WERE NOT USED IN CLINICAL TRIALS:

The sponsor proposes to market four strengths of venlafaxine ER capsules, 37.5, 75, 100 and 150 mg. The 75 and 150 mg strengths have been tested for bioavailability. The sponsor is requesting a bio-waiver for the 37.5 and 100 mg strengths based on in vitro dissolution data and the IVIVC developed. All the four strengths are compositionally proportional. Each strength contains the same coated spheroids in varying quantities (proportional to each strength).

Since these strengths are compositionally proportional containing the same spheroids, waiver can be granted based on in vitro dissolution. The sponsor has submitted dissolution data obtained using the selected dissolution testing method, for 3 batches (testing on 12 units/batch) each for the 37.5 and 100 mg strengths. The batch size for the 37.5 mg strength ranged from capsules and for the 100 mg strength ranged from capsules. The mean (% CV) for the 3 batches each of 37.5 and 100 mg strengths and for the 75 and 150 mg strengths that were used in the pivotal biostudy are shown in the following table:

Time in hours	Mean % (% CV) venlafaxine dissolved							
	37.5 mg	37.5 mg	37.5 mg	75 mg	100 mg	100 mg	100 mg	150 mg
2	25 (5.8)	26 (11.8)	23 (21.4)	22 (12.8)	17 (11.3)	16 (7.8)	16 (10.7)	16 (5.9)
4	50 (4.1)	52 (7.4)	49 (12.8)	45 (4.8)	42 (3)	40 (4)	43 (5.2)	41 (2.7)
8	73 (3.5)	73 (6.0)	72 (9.1)	68 (3.4)	68 (2.6)	64 (2.8)	70 (3.2)	67 (2.7)
12	83 (3.7)	81 (5.6)	82 (8.4)	80 (2.9)	80 (2.5)	76 (2.4)	82 (3.2)	79 (3)
24	95 (3.6)	91 (4.8)	94 (7.6)	93 (2.5)	93 (2.5)	89 (2.2)	93 (2.9)	93 (2.9)

Following figure shows the dissolution profiles for the 4 strengths of venlafaxine ER capsules:



CONCLUSION: The dissolution profiles for all the four strengths are similar and meet the selected dissolution specifications. Hence, a biowaiver can be granted for the 37.5 and 100 mg strengths of venlafaxine ER capsules.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20699

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-677 SUPPL #_____

Trade Name Effexor XR **Generic Name** Venlafaxine HCl Sustained Release
Applicant Name Wyeth Ayerst **HFD-** 120

Approval Date 10-20-97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /✓/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Did not state

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ✓ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-151 Effexor (Venlafaxine HCl) Immediate Release

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ✓ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /__/

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If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 600-B-208-US

Investigation #2, Study # 600-B-209-US

Investigation #3, Study # 600-B-367-UK

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3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # 600-B-208-US

Investigation #_, Study # 600-B-209-US

Investigation #_, Study # 600-B-362-UK

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND YES /✓/ NO /___/ Explain: ____

Investigation #2

IND # YES /✓/ NO /___/ Explain: ____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

Signature Date 2/26/97

Title: Project Manager

Signature of Division Director Date 8/15/97

cc: Original NDA Division File HFD-85 Mary Ann Holovac

(637)

OUTGOING

REQUEST FOR TRADEMARK REVIEW

MAY 30 1996

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Neuropharmacological Drug Products HFD-120	
Attention: Paul David, Project Manager	**Phone:** (301) 594-5530
Date: May 28, 1996	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Effexor XR Extended Release capsules	**NDA#** 20-699
Established name, including dosage form: venlafaxine HCl capsules	
Other trademarks by the same firm for companion products: Effexor Tablets	
Indications for Use (may be a summary if proposed statement is lengthy): Depression,	
Initial Comments from the submitter (concerns, observations, etc.): Attached is the draft labeling submitted by W-A, for this original NDA. The marketed immediate-release formulation, NDA 20-151, is dosed 2-3 times daily. The Division does not have any concerns with the proposed trade name. Please review the sponsor's proposed trade name for acceptability.	

DETROIT

AUG 06 1996

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-699; HFD-120/Division file; HFD-120/P.David; HFD-120/PLeber/TLaughren/GDubitsky

Rev. December 95

5-22-96

Consult #637 (HFD-120)

EFFEXOR XR venlafaxine HCl extended-release capsules

Since Effexor Tablets is a marketed product, the Committee considered the acceptability of the suffix "XR". The Committee notes that the suffix stands for "Extended-release", and believes this is a meaningful modifier that would differentiate this product from the other EFFEXOR products.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

D L Boring 8/1/96, Chair

M E M O R A N D U M

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

9-12-97 I agree with the reviewer's proposal in this memo. See 9-12-97 memo. *

DATE: September 11, 1997

TO: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products Group
Division of Neuropharmacological Drug Products

FROM: Gregory M. Dubitsky, M.D.
Clinical Reviewer, Psychiatric Drug Products Group
Division of Neuropharmacological Drug Products

SUBJECT: NDA 20,699 (Effexor XR for depression):
Adverse event pooling in product labeling

I. Background

The safety database for the Effexor XR depression NDA (#20,699) contained a total of three short-term, placebo-controlled studies: two U.S. studies (208 and 209) and one European study (367). The sponsor has proposed that discussions and displays of adverse event information in labeling be based on the pool of all three studies. This memorandum explicates my choice of the study pool for review safety analyses and for data presentations in product labeling.

Given that point estimates of adverse event incidence in clinical trials are known to be highly variable across studies, this discussion will focus on accepted criteria for judging the common occurrence and likely drug relatedness of events, e.g., those events occurring in at least 5% of drug patients at a rate at least twice that of placebo. Such criteria are thought to produce more stable representations of adverse event profiles. An important caveat, however, is that these criteria are arbitrarily established and, generally being based on unstable point estimates, produce profiles which themselves can be quite variable across studies.

II. Pooling Considerations

Characteristics of these studies are summarized in the appended Table 1. Adverse event information in all three trials was

elicited in similar fashion.[1] Since there exist design differences between these studies which lead one to question their poolability, the comparability of adverse experience occurrence was evaluated among these studies in a preliminary manner by considering those events that occurred in at least 10% of drug patients at a rate at least twice that of placebo group. The listings of events meeting these criteria are provided by study in Table 2.

Clearly, there is a difference in the number of events meeting these criteria among the studies, with both U.S. trials associated with at least three times the number of such events as the European trial. Given the possibility that the domestic study pool of studies 208 and 209 might be preferable as a basis for the safety review of this NDA, the Team Leader, Dr. Laughren, was consulted on November 22, 1996, for his advice on this issue. After considering the above information, he opined that the pool of the two U.S. studies was preferable to the pool of domestic and foreign studies. Thus, the safety analyses in the clinical review of this NDA focused on the pool of the two U.S. studies.

Further support for the selection of this pool emerged during the evaluation of events leading to premature discontinuation and events considered common and drug related (i.e., events occurring in ≥5% of Effexor XR patients at a rate at least twice the placebo rate). The listings of such events for the domestic study pool was discovered to be larger than the list for the three study pool, especially for the drug-related events (see the appended Table 3).

On the basis of these data, I previously recommended that the pool of studies 208 and 209 provide the basis for safety data displays in product labeling and, thus, the labeling issued with the approvable letter for this NDA was based on the pool of these two domestic studies.

The sponsor objected to the omission of study 367 from the safety data pool, arguing that: 1) the three study pool reflected a "broader" range of experience with Effexor XR; 2) there were no known differences in adverse event data collection, coding, or analysis between the U.S. and foreign studies; 3) that a comparison of the odds ratios for several common events across the three individual studies revealed a statistically significant difference for only one event, dry mouth; 4) the incidence data from the total pool was more consistent with that previously documented for the immediate release formulation of Effexor; and

---

[1]Data was based on signs and symptoms reported by the patient or observed by the investigator during each evaluation in addition to the patient's response to the non-specific question "How have you been feeling since your last visit?"

Regulatory guidance with respect to the Adverse Reactions section of drug labeling (21 CFR 201.57(g)) does not specifically address the issue of pooling studies. Similarly, guidance regarding NDA content and format for clinical data (21 CFR 314.50(d)(5)) is silent on the matter of pooling. In addition, there is no known formal guidance within the Center for objectively evaluating the appropriateness of pooling strategies.

Less formally, the following elements have been considered by many to be reasonable criteria for judging poolability: overall study design features (randomization, blinding, crossover), dose and dosing regimen (fixed vs. flexible), trial duration, method of eliciting adverse events, and adverse event incidence.[2] But these criteria are not easily applied to the three studies under consideration: neither the pool of all three nor any combination of two of these studies are comfortably poolable because of differences in key features (see Table 1). While one could advocate selecting just one study as the basis for analyzing safety data, one is then left with the problem of deciding which one; also, it could be countered that such an approach excludes most of the controlled safety data and, if there were an inclination to apply statistical testing, would markedly limit the power to detect statistically significant differences in occurrence between drug and placebo.

In sum, there is clearly a difference in the adverse event profile for Effexor XR, as defined by those events considered common and drug-related, between the pool of the three placebo-controlled studies and the pool of U.S. studies excluding the foreign study. Adverse experience in pools consisting of one of the U.S. studies with the foreign study (i.e., 208/367 and 209/367) have not been examined although, by design features, they could have been equally considered despite the somewhat greater similarity in event profiles between the two U.S. studies (Table 2). While a tradition of conservatism with respect to safety and a degree of underlying, but unproven, suspiciousness of foreign data would lead one to prefer the U.S. study pool, it is difficult to justify this choice objectively.

III. Recommendations

Considering the above, the use of the pool of studies 208, 209, and 367 as a basis for presenting safety data in labeling is not considered unreasonable. I feel that the different adverse event profile seen when the two U.S. studies (208 and 209) are pooled

---

[2]The last factor has arguable validity for assessing poolability because it seems to presume, without basis, that excluded data is irrelevant. The exception is data which is markedly discrepant from the vast bulk of the experience with the drug.

can be adequately noted in labeling as a footnote to the table of adverse dropouts and as an addition to the listing of common, drug-related events.

The converse would be acceptable, that is, using the U.S. pool for the primary data presentations with additional annotation of differences from the three study pool. However, in view of the sponsor's preference for the three study pool and the lack of an objective argument which clearly favors the domestic pool, this approach is not preferred.

Table 1: Study Characteristics

Study	Location	Dosing Regimen	Doses (mg/day)	Duration (weeks)	N_{EffXR}
208	U.S.	Flexible	75-150	12	97
209	U.S.	Flexible	75-225	8	95
367	Europe	Fixed	75, 150	8	83(75mg) 82(150mg)

Table 2: Adverse Events Occurring in ≥10% of Effexor XR Patients at a Rate ≥2X Placebo

208	209	367
Anorexia	Anorexia	
Constipation		
Diarrhea		
Dry mouth	Dry mouth	
Nausea	Nausea	Nausea
Abnormal dreams		
Dizziness		
Somnolence	Somnolence	Somnolence
Sweating	Sweating	Sweating
Abn. ejaculation/orgasm	Abn. ejaculation/orgasm	
	Insomnia	
	Nervousness	
	Impotence	

Table 3: Effect of Pooling Strategy on Adverse Event Listings in Effexor XR Labeling *		
Listing	Study Pool	
	208, 209, & 367 Neff = 357	208 & 209 Neff = 192
Common Adverse Events Leading to Discontinuation	Nausea Anorexia Dry Mouth **Dizziness** Insomnia **Somnolence**	Nausea Anorexia Dry Mouth Insomnia **Hypertension** **Diarrhea** **Paresthesia** **Tremor** **Blurred vision** **Delayed Ejaculation**
Common, Drug-Related Adverse Events	Abnormal ejaculation Nausea Dry Mouth Anorexia Dizziness Somnolence Abnormal dreams Sweating	Abnormal ejaculation Nausea Dry Mouth Anorexia Dizziness Somnolence Abnormal dreams Sweating **Abnormal orgasm** **Abnormal vision** **Constipation** **Flatulence** **Hypertension** **Impotence** **Insomnia** **Libido decreased** **Nervousness** **Tremor** **Vasodilatation** **Yawning**

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

Table 4: Adverse Events Occurring in ≥5% of Effexor XR Patients at a Rate ≥2X Placebo in Study 367, by Dose	
75 mg/day	150 mg/day
Accidental injury Asthenia Hypertension Dry mouth Nausea Weight gain Somnolence Pharyngitis Sweating	Dry mouth Nausea Somnolence Sweating Abn. Ejaculation

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 20, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Approval Action Memorandum
NDA 20-699: Effexor XR ™, Wyeth-Ayerst Laboratories brand of venlafaxine HCl extended release capsules [37.5,75,100, & 150 mg]

TO: File NDA 20-699

This memorandum records for the administrative file my decision to approve Wyeth-Ayerst's NDA 20-699 for Effexor-XR. The application allows for the marketing of an extended release formulation of venlafaxine, an antidepressant drug product, under a claimed use essentially identical to that granted to the already marketed IR formulation, Effexor.

The NDA was declared approvable in an action letter issued on 5/2/97 by the Office Director, Dr. Temple. My comments and observations on the evidence supporting the approvable action are provided in my memorandum of April 8, 1997.

Post-Approvable Review Activities.

The Office Director delegated (by verbal communication at administrative rounds) to the Director of DNDP responsibility for all subsequent regulatory action affecting the status of the NDA.

Safety Update [SU], Foreign Regulatory Update & World Literature review

The SU covers the interval from 12/31/95 to 9/30/96. The primary review of the SU, foreign regulatory update, and the World Literature review was carried out by Dr. Dubitsky (May 28, 1997). Dr. Dubitsky

concludes that these reports provide no finding that would cause the agency to modify its prior conclusion that Effexor-XR has, within the meaning of the Act, been shown to be safe for use. Dr. Laughren, the Team Leader for DNDP's Psychopharmacology Unit, affirms his conclusion.

Labeling

The version of Effexor-XR product labeling forwarded as an attachment to the approval action letter intended for issuance under my signature was developed under the leadership of Dr. Laughren.

This version does not differ substantively from the draft attached to the approvable action letter; the modifications that have been made are jointly acceptable to both the sponsor and the Division's review team(see Dr. Dubitsky's 8/13/97 review and Dr. Laughren's Team leader's memorandum of 9/12/97).

Post- Marketing Commitment.

The firm, as requested in the agency's approvable action letter, has agreed to conduct a In fact, the trial is already underway.

Dissolution Specifications and CMC

The sponsor has agreed to adopt dissolution specifications that are acceptable to staff of the Division of Biopharmaceutics. These specifications are enumerated in the text of the approvalaction letter.

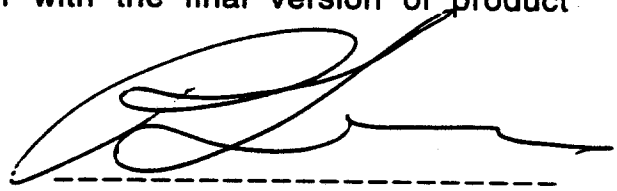
The sponsor has been granted a 24 month expiry date for the product, although final validation of regulatory methods is still pending (Center policy allows NDA approval in the face of this deficiency, however).

Conclusion

The review team's analyses of the information provided in the application support approval of the NDA.

Action Taken

Issuance of the approval action letter with the final version of product labeling attached.



Paul Leber, M.D.
October 20, 1997

cc:
NDA 20-699

HFD-101
Temple
HFD-120
Katz
Laughren
Dubitsky
Fitzgerald
Steel
Guzewska
Heimann
David
HFD-860
Baweja

M E M O R A N D U M

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

DATE: September 12, 1997

FROM: Thomas P. Laughren, M.D. Thomas P. Laughren, MD
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Effexor XR (venlafaxine extended release) for the treatment of depression

TO: File NDA 20-699
[**Note:** This overview should be filed with the 5-15-97 submission.]

1.0 BACKGROUND

In our 5-2-97 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, and a commitment to conduct . In the biopharmaceutics area, we identified our preferred dissolution methodology and specifications. We also attached our proposal for labeling. Wyeth-Ayerst responded formally to the approvable letter with (1) a 5-15-97 submission addressing all issues except labeling, and (2) a 6-12-97 submission including revised labeling.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks to arrive at the version of labeling [LABFXRDP.AP5] that is included with the approval letter.

Dr. Gregory Dubitsky reviewed the clinical sections of the 5-15-97 and 6-12-97 responses to the approvable letter, including the safety update, the literature update, the regulatory status update, and revised labeling.

2.0 SAFETY UPDATE

The safety update included reports of death, serious adverse events, and adverse dropouts, covering a period from 12-31-95 through 9-30-96. These included reports from 2 completed extension studies and 14 ongoing, unblinded studies. There was one additional death, from pneumonia in an 89 year old woman 2 months after discontinuing drug. There were 28 additional serious adverse events, only 1 of which Dr. Dubitsky considered even possibly related to venlafaxine treatment, i.e., a case of closed angle glaucoma. This event will be mentioned in the "Other Events" table. Dr. Dubitsky also reviewed and commented on adverse dropouts from this expanded database. In summary, none of these reports contained new or unusual findings that would change my view about the approvability of this drug or necessitate further labeling changes, except for the instance noted.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period through 3-17-97, revealing only 4 relevant publications. Dr. Aguiar of Wyeth-Ayerst reviewed these articles and warranted that they contained no findings that would adversely affect conclusions about the safety of Effexor XR.

4.0 FOREIGN REGULATORY UPDATE

Applications for Effexor XR are pending in 19 foreign countries, but it is not yet approved anywhere. The sponsor warranted in the 5-15-97 submission that no negative regulatory actions have been taken with regard to this drug.

6.0 BIOPHARMACEUTICS

The sponsor accepted our proposed dissolution method and specifications.

7.0 LABELING

Wyeth Ayerst proposed several changes to the labeling for Effexor XR, some of which we found acceptable, while others were the subject of negotiations with the review team over a roughly 3-week time period, as noted under Background. The issue requiring the greatest effort to resolve was one of which pool of studies to rely on in constructing adverse event tables in labeling. The agreement worked out, one which is satisfactory to me, was to permit the sponsor to utilize all 3 studies for the tables, but to acknowledge in narrative form additional events identified from the 2-study US pool that either led to dropout or that met our criteria for being common and drug related. We were able to reach agreement at a Team Leader level on labeling, and thus, the version of labeling accompanying the approval letter represents a mutually agreed upon document.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth-Ayerst has submitted sufficient data to support the conclusion that Effexor XR is effective and acceptably safe in the treatment of depression. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 20-415
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/PDavid

DOC: MEMFXRDP.AP1

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 8, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Approvable Action Memorandum
NDA 20-699: Effexor XR ™, Wyeth-Ayerst Laboratories brand of venlafaxine HCl extended release capsules [37.5,75,100, & 150 mg]

TO: File NDA 20-699
&
Robert Temple, M. D.
Director,
Office of Drug Evaluation, HFD-101

This memorandum conveys my recommendation to declare NDA 20-699, submitted on 5/16/96, approvable.

Background:

The current application seeks approval for an extended release oral formulation of venlafaxine intended for administration on once a day dosing schedule; the NDA for Effexor [NDA 20-151], an immediate release [IR] formulation of the drug was approved for the product's use as an antidepressant in December of 1993. The IR formulation is recommended for use on a bid or tid schedule.

The administrative history of the application is covered in Dr. Laughren's 3/7/97 supervisory overview. It is noteworthy that the Division initially considered evaluating the safety and effectiveness of Effexor XR on bioequivalence criteria[1] alone, but, because of unresolved concerns about the validity of the approach, we ultimately advised the sponsor that

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[1] Declaring the products therapeutically fungible if equal molar doses 1) generated identical parent AUCs and 2) ([Cmax-Cmin]/[C average]) ER ≤ ([Cmax-Cmin]/[C average]) IR.

evidence from controlled clinical trials would eliminate the need to mount a persuasive argument that drug input rate and plasma concentration fluctuation do not affect the efficacy of an antidepressant drug.

Review Issues:

Efficacy in use:

As intended by its developers, Effexor XR, when administered at an equivalent molar dose on a once a day dosing regimen delivers the same amount of venlafaxine to the systemic circulation as Effexor IR when the latter is given in divided daily doses (i.e., AUC equivalence), but, with a lower Cmax and equivalent Cmin (less fluctuation). As implied earlier, this evidence alone would probably be sufficient to persuade some, but by no means all, experts that Effexor XR is the therapeutic equivalent of Effexor IR in regard to its efficacy as an antidepressant. The results of 2 adequate and well controlled clinical investigations, **Studies 208 and 209**, remove the need for speculation, providing persuasive evidence that the ER formulation is, within the meaning of the Act, effective in use. The Table below outlines the results of the 2 positive RCTs,

Study	ER doses/ [mean dose]	Active control {AC} :dose [mean dose]	Du-ra-tion	# R/F on ER	# R/F on AC	# on R/F Pbo	Treatments statistically superior to placebo at 12 weeks [208] 8 weeks [209]
#208 12 cen-ter	75-150 mg/day [138 mg]	Effexor IR: 75-100mg [117 mg]	12 wk	49/ 85	39/ 81	43/ 91	ER, IR > Pbo on HAM-D tot, HAM D item 1, CGI on LOCF and OC
#209	75-225 mg/day [177 mg]	N.A.	8 wk	60/ 91	N.A.	51/ 100	ER> Pbo on HAM-D tot, HAM D item 1, CGI on LOCF --OC spotty

N.B. Mean dose is dose among 12 week [208] or 8 week [209] completers; R/F is number randomized /number completing **6 weeks.**

A third trial, **Study 367**, an 8 week long investigation comparing 2 fixed doses of Effexor XR (75 mg and 150 mg a day) with paroxetine (20 mg a day) and with placebo, however, failed to detect an antidepressant effect of any active drug treatment arm, and must, therefore, be deemed a "failed[2]" study.

The outcome of 367, incidentally, is but another illustration of why I find it ill-advised to treat the numerical value of an effect size estimate adduced in a positive clinical trial intended to contribute evidence to meet the burden of substantial evidence as a basis to estimate the expected effect[3] of a drug in the population. While the 'null' outcome of study 367 is ignorable in regard to the regulatory determination as to whether or not there is "proof in principle" of Effexor XR's effectiveness as an antidepressant, the outcome of study 367 cannot be set aside when one seeks to estimate the average (expected) size of its effect in depressed patients.

Finally, as Dr. Laughren notes, the evidence developed in clinical studies with the ER product provides no additional insights into the relationship between administered daily dose and response (benefit or risk).

Safety for Use.

Within the meaning of the Act, Effexor XR is 'safe for use.' This conclusion relies upon experience gained with the now approved IR product and with product specific experience gained in the development of Effexor XR.

In offering this view, I am mindful that clinical experience gained with the some 850 patients who received 1 or more doses of Effexor XR is

---

[2] Because the active standard control treatment, paroxetine, could not be discriminated from placebo, the study cannot be viewed as one possessing a capacity to detect an antidepressant drug effect. Accordingly, the study is considered "failed," rather than "negative," and it is discounted as a source of probative evidence counting either for or against the drug.

[3] if, in fact, such an effect parameter can be claimed to exist in any valid sense.

highly unlikely to provide new insights into the risks associated with the use of venlafaxine. In fact, had we been persuaded that rate of input of venlafaxine was unimportant to its effectiveness in use, we would in all likelihood have concluded that experience with the IR product was sufficient to support a conclusion that the extended release was safe for use.

These arguments cut in the reverse direction, as well, however. Clinical experience gained with Effexor XR does not provide a sufficient basis to cause modification of any views now extant about venlafaxine, save, perhaps, that rate of its systemic input does not have a critical effect on its efficacy. It may be, of course, .that the realized differences between the pharmacokinetic performances of the ER and IR products systematically affect some consequence of exposure to venlafaxine, but absent a head to head comparison of the IR and ER products in a suitable controlled experiment, the nature of these differences, if any, will remain unknown.

Labeling issues

The labeling the sponsor proposes for Effexor XR differs from that of the already marketed product, Effexor in a number of ways. Some differences are appropriate and necessary, addressing specific matters that are unique to each product (e.g., PK differences, dosing recommendations, capsule size, etc., description of clinical trials supporting approval, etc). There are, in addition, however, a number of differences in the labeling that appear to reflect an attempt by the sponsor to modify the way in which the risks and benefits of venlafaxine, the drug substance, are presented.

In his excellent supervisory memorandum of 3/7/97, Dr. Laughren reviews and explains why he believes the agency ought not to agree to the text of Effexor XR labeling as proposed by the sponsor. I find his arguments persuasive and favor the adoption of his counter-proposal for labeling; it will allow Effexor XR to be marketed with claims that are neither false nor misleading entirely reasonable. Accordingly, the adoption of the draft labeling developed by the Division (attached to the Approvable Action letter) is identified as a condition of approval of the Effexor XR NDA.

Conclusion:

The application is approvable.

Recommendation:

Issue the approvable action letter.

4/8/97

Paul Leber, M.D.
April 8, 1997

cc: NDA 20-699
cc:
HFD-101
Temple
HFD-120
Katz
Laughren
Dubitsky
Fitzgerald
Steel
Blum
Guzewska
David
HFD-710
Salhroot
Choudhury
HFD-860
Baweja

M E M O R A N D U M

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

DATE: April 16, 1997

FROM: Director, Office of Drug Evaluation I

SUBJECT: Effexor XR, NDA 20-699

TO: Dr. Leber
Dr. Laughren

There are, as you and Drs. Laughren and Feeney note in excellent reviews, sufficient data to support approval of sustained-release venlaflexine, although the dose-response remains elusive. I have just a few comments and questions:

1. Note Dr. DeGeorge's suggestions re the Repro and Carcinogenicity sections.

2. MOR page 9 has M/F reversed.

3. See my comments on Clin Pharm labeling. As usual, I have tried to compress this section. See what you think.

4. Tom's memo had suggested he might urge limiting indications to moderate depression and emphasize the lack of experience in severe depression. Labeling does mention lack of in-patient experience, but not these other points. Does it cover this issue adequately.

5. With respect to the letter (page 2), you don't really need narratives for all adverse drop-outs, only those of special interest. (See E-3 Guideline), (page 3, section 12.3.2.

6. Should the ADR section also reflect results of the additional controlled studies now available (I've seen a review of two more)? If so, letter and labeling should mention that. Also, given only 200 people/group in the table, consider making it a 2% table. Events

occurring in 3-4 people probably don't deserve this level of attention. If you change this, you'd need to change page 26 too.

7. Shouldn't table four precede table three (that's how you usually do it), so that you have an order of importance: ADR's causing DC, high rate events increased compared to placebo, table of 2% (or 1%), all else. Also, is table four really needed at all? Everything in it is already in table three. An alternative is a paragraph before table three that highlights the important ADR's, e.g., just before table three, something like: Note in particular the following adverse events that occurred in at least 5% of Effexor XR patients and at a rate at least twice that of the placebo group: Abnormalities of sexual function (abnormal ejaculation and abnormal orgasm in both men and women, impotence, and decreased libido), gastrointestinal complaints (nausea, dry mouth, constipation, anorexia, and flatulence), CNS complaints (dizziness, insomnia, somnolence, nervousness, abnormal dreams, tremor), problems of special senses (blurred vision and difficulty focusing eyes) sweating, yawning, and cardiovascular effects (hypertension and vasodilation).

8. Finally, I note one policy point related to Tom's review (page 2). We have not, to my best knowledge, ever had a policy of either requiring or not requiring clinical data in support of an ER formulation of an approved IR drug. This has always been a judgement call. There has been an attempt to evolve a policy (when would we and wouldn't we need trials) but the draft report has not been acted on, and certainly cannot be considered final. Indeed, within recent memory your division has concluded that clinical studies of certain ER anti-seizure drugs were not needed. The recent "Providing Clinical Evidence of Effectiveness" guidance provides pertinent policy, as it strongly suggests a single persuasive study in this case is sufficient, but it too does not address the question of when a clinical study is needed.

Robert Temple

Robert Temple, M.D.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-699 Supplement #____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-120; Trade (generic) name/dosage form: Effexor XR (venlafaxine hydrochloride) extended release capsules Action: AP

Applicant Wyeth-Averst Therapeutic Class 3S

Indication(s) previously approved None
Pediatric labeling of approved indication(s) is adequate ___ inadequate N/A

Indication in this application Depression
____ (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

X b. The applicant has committed to doing such studies as will be required.
- X (1) Studies are ongoing,*
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

* WA is conducting pediatric studies, as a Phase 4 commitment, as part of the approval of the immediate release formulation of venlafaxine HCl (NDA 20-151). The Agency agreed with the sponsor's request to use the extended release formulation of venlafaxine to meet this Phase 4 commitment. Therefore, WA has an ongoing study in the pediatric population with the extended release venlafaxine to fulfill this Phase 4 commitment.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Project Manager 9/10/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-699
HFD-120/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)