Relative Bioavailability of Two Formulations of Venlafaxine Extended-Release 75-mg Capsules in Healthy Brazilian Male Volunteers: A Single-Dose, Randomized-Sequence, Open-Label, Two-Period Crossover Study in the Fasting and Fed States

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ABSTRACT

Background: The oral antidepressant venlafaxine hydrochloride is a selective serotonin–norepinephrine reuptake inhibitor.

Objective: The aim of this study was to evaluate the bioequivalence of a new generic formulation of venlafaxine extended-release 75-mg capsules (test) and the available branded formulation (reference) to comply with regulatory criteria for marketing of the test product in Brazil.

Methods: This single-dose, randomized-sequence, open-label, 2-period crossover study was conducted in healthy male volunteers and consisted of separate fasting and fed phases. A single oral dose of the test or reference formulation was followed by a 7-day washout period, after which subjects received the alternative formulation. There was a 3-month interval between the fasting and fed portions of the study. There was no standardization of race because of the difficulty of achieving standardization in the Brazilian population. Blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours after dosing. Venlafaxine concentrations were determined using an HPLC-MS/MS method. The formulations were considered bioequivalent if the 90% CIs of the geometric mean ratios (test:reference) for C_{max} and AUC_{0-t} were within the regulatory range of 80% to 125%. Adverse events were monitored throughout the study based on vital signs, laboratory tests, interviews, and spontaneous patient reports.

Results: Forty-eight subjects were enrolled in both phases of the study; all 48 subjects completed the fasting phase, and 1 subject withdrew during the fed phase. The mean (SD) age of participants in the fasting and fed phases was 24.96 (5.5) and 24.90 (4.7) years, respectively; their mean weight was 69.65 (9.6) and 71.00 (10.6) kg and their mean height was 172.0 (6.9) and 173.0 (6.6) cm. Under fasting conditions, the arithmetic mean venlafaxine C_{max} was 35.705 (23.946) ng/mL for the test formulation and 34.470 (20.639) ng/mL for the reference formulation, with a geometric mean ratio of 1.04. The arithmetic mean AUC_{0-t} for the respective formulations was 562.015 (481.875) and 508.509 (439.456) ng · h/mL, with a geometric mean ratio of 1.11. The arithmetic mean T_{max} was 6.188 (1.560) and 5.885 (1.648) hours. Under fed conditions, the arithmetic mean venlafaxine C_{max} was 42.892 (24.348) ng/mL for the test formulation and 46.275 (23.011) ng/mL for the reference formulation, with a geometric mean ratio of 0.93. The arithmetic mean AUC_{0-t} for the respective formulations was 737.218 (603.998) and 682.124 (524.713) ng · h/mL, with a geometric mean ratio of 1.08. The arithmetic mean T_{max} was 6.787 (1.769) and 5.957 (1.661) hours. There were no significant increases

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in venlafaxine C_{max}, AUC_{0-t}, or T_{max} for either formulation in the fed phase compared with the fasting phase. In both the fasting and fed portions of the study, the 90% CIs for the ratio (test:reference) of log-transformed C_{max} (fasting: 93.24–105.93; fed: 84.67–97.85) and AUC_{0-t} (fasting: 102.90–116.71; fed: 98.19–114.41) were within the acceptance range for bioequivalence. The most common adverse events (≥5% of subjects) in the fasting phase were nausea (46%), diarrhea (29%), headache (29%), vomiting (15%), and colic (6%); the most common adverse events in the fed phase were nausea (15%), headache (13%), and dizziness (9%).

Conclusion: In this single-dose study in healthy fasting and fed volunteers, the test formulation of venlafaxine extended-release 75-mg capsules met Brazilian regulatory criteria for bioequivalence to the reference formulation. (*Clin Ther.* 2010;32:2088–2096) © 2010 Elsevier HS Journals, Inc.

Key words: venlafaxine, extended release, fed, fasting, bioequivalence, pharmacokinetics.

INTRODUCTION

The oral antidepressant venlafaxine hydrochloride is a phenylethylamine-derived selective serotonin–norepinephrine reuptake inhibitor. This antidepressant class was developed to avoid certain effects of the tertiary-amine tricyclic antidepressants, such as blocking of muscarinic, histaminergic, and adrenergic neuroreceptors and inhibition of fast sodium channels.[1–7]

Venlafaxine has been reported to be well absorbed after oral administration (~92%). Metabolism of venlafaxine occurs primarily via O-demethylation (mediated by cytochrome P450 [CYP] 2D6) and, to a lesser extent, by N-demethylation (mediated by CYP3A4).[8] Approximately 5% of an administered dose is excreted in the urine as unchanged drug, with <30% excreted as an active metabolite, O-desmethylvenlafaxine.[9] Metabolism has been reported to be linear at venlafaxine doses up to 225 mg/d.[10] At steady state, the $t_{1/2}$ of venlafaxine is ~5 hours and that of O-desmethylvenlafaxine is ~11 hours, necessitating administration 2 or 3 times daily to maintain adequate plasma drug concentrations.[11] A microencapsulated, extended-release formulation of venlafaxine was developed to allow once-daily administration.[12]*

*Trademark: Effexor XR® (Wyeth Pharmaceuticals Company, Inc., Guayama, Puerto Rico).

A new generic formulation of venlafaxine extended-release 75-mg capsules has been developed (Cristália Produtos Químicos Farmacêuticos Ltda., Itapira, São Paulo, Brazil). The present study was conducted to determine whether the relative bioavailability of the test formulation met Brazilian regulatory criteria for the assumption of bioequivalence to the branded formulation.

SUBJECTS AND METHODS

Inclusion and Exclusion Criteria

Healthy Brazilian male volunteers aged 18 to 45 years, with a body mass index of 18 to 29 kg/m^2, were eligible for participation in the study. There was no standardization of race, because of the difficulty of achieving standardization in the Brazilian population. Subjects underwent screening examinations that included a medical history, physical examination, vital signs (blood pressure, heart rate, body temperature), and laboratory tests (hemoglobin, hematocrit, total white blood cell count with differential, blood glucose, triglycerides, total cholesterol, albumin, direct and indirect bilirubin, creatinine, aspartate and alanine aminotransferase, γ-glutamyltransferase, urinalysis, and testing for HIV and hepatitis B and C antibodies), all of which were performed at CERPE Diagnósticos Ltda. (Recife, Pernambuco, Brazil). A 12-lead ECG was also obtained.

Exclusion criteria included medically documented cardiovascular, respiratory, renal, hepatic, or gastrointestinal disorders; a chronic disorder that might affect the absorption, disposition, metabolism, or excretion of venlafaxine; a history of hypersensitivity to venlafaxine or other drugs; a history of alcohol or drug abuse; participation in another clinical trial within 3 months; smoking; daily consumption of >4 glasses of beverages containing xanthine derivatives; and use of any medication having the potential to affect the study results within 10 days before the start of the study.

The purpose of the study was explained to volunteers before the study, and written informed consent was obtained from all subjects before they underwent any study procedures.

Study Design and Procedures

This single-dose, randomized-sequence, open-label, 2-period crossover study was conducted between February and May 2008. It consisted of separate fasting and fed phases. In each phase, subjects were ran-

domly assigned to receive a single capsule of either the test or reference formulation during the first period and the alternative formulation during the second period. The periods were separated by a 7-day washout period. There was a 3-month interval between the fasting and fed phases of the study. The reference drug was purchased from a pharmacy, and the test drug was provided by Cristália Produtos Químicos Farmacêuticos Ltda.

Volunteers were admitted to the clinical trial center (Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Pernambuco, Brazil) at 7 PM on the day before administration of each dose of study drug and were confined to the center for 48 hours after administration of each dose. In the 24 hours after drug administration, subjects received a standardized lunch, snack, and dinner (2300 kcal/d; 50% carbohydrate, 20% protein, 30% fat) at ~11 AM, 4 PM, and 8 PM, respectively. All meals were planned by a nutritionist, and standardized meals consisted of the same foods in both phases in the study. Throughout their stay at the center, subjects were monitored by a multidisciplinary team of 4 pharmacists, 2 physicians, and 2 nurses.

Doses of the study drugs were administered with 300 mL of water at 8 AM on the day after admission. In the fasting phase, subjects received a single 75-mg capsule of the test or reference formulation, having consumed no food since the previous night's dinner. In the fed phase, subjects received a standardized breakfast 30 minutes before drug administration. Mouth and hand checks were performed after administration of each dose to ensure that all medication had been ingested. Food and drink were prohibited for 3 hours after dosing; water was prohibited during the first hour after dosing. Xanthine-containing products were not allowed from 2 days before dosing to 48 hours after dosing.

The study protocol was reviewed and approved by the research ethics committee of the Universidade Federal de Pernambuco and conducted in accordance with the Declaration of Helsinki (revised, South Korea 2008) and the International Conference on Harmonisation Good Clinical Practice guidelines. The study was conducted in accordance with Agência Nacional de Vigilância Sanitária (ANVISA) guidelines for relative bioavailability/bioequivalence studies,[13] which are identical to those of the US Food and Drug Administration (FDA).[14] Volunteers were compensated for their participation in the study.

Tolerability

Adverse events (AEs) were collected based on questioning of subjects and spontaneous reports, as well as monitoring of vital signs (blood pressure, heart rate, body temperature, and respiratory rate). Sitting blood pressure and heart rate were measured by standard methods before dosing and 4, 8, and 12 hours (±30 minutes) after administration of each dose of study medication and before release from the clinical facility. Laboratory tests (hematology, biochemistry, liver function, and urinalysis) were performed at baseline and at the end of each phase, and were reviewed by the clinical investigators. Other exit procedures included general observation, physical examinations, and measurement of vital signs.

Blood Sampling and Preparation

Blood samples (8 mL) were collected from an indwelling catheter (BD Angiocath, Becton, Dickinson and Company, Franklin Lakes, New Jersey) in the antecubital forearm vein. Samples were obtained before each dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours after dosing. After collection of each sample, the catheter was flushed with 1 mL of heparinized saline (Blausiegel Ind. E Com. Ltda., Cotia, Brazil) 10 IU/mL. Blood samples were immediately transferred to two 4-mL EDTA-containing tubes (ZheJiang GongDong Medical Technology Company, Ltd., Taizhou, Zhejiang, China) and centrifuged (JOUAN SA, Saint-Herblain, France) at room temperature for 5 minutes at 1350*g*. Plasma was transferred to cryogenic tubes with disposable polypropylene tips and stored frozen at –70°C until analyzed.

Stock solutions of venlafaxine at 1.0 mg/mL (European Pharmacopoeia, lot 1) were prepared by dissolving the substance in acetonitrile:water (1:1 v/v). Stock solution of fluoxetine (lot F2C132, Cristália), the internal standard, was prepared at 1.0 mg · mL^{-1} in acetonitrile. Working solutions of venlafaxine were prepared in mobile phase to provide concentrations ranging from 0.10 to 70 ng/mL. Internal standard working solution was prepared in mobile phase at a concentration of 1000 ng/mL. The calibration curves for venlafaxine were prepared in human plasma (Fundação de Hematologia e Hemoterapia de Pernambuco, Recife, Pernambuco, Brazil) at concentrations of 1, 3, 5, 10, 20, 40, and 70 ng/mL. Quality-control samples were prepared in human plasma at concentrations of 3, 30, and 60 ng/mL (low, medium, and high, respectively).

Plasma samples (400 μL) were transferred to 2-mL polypropylene vials, to which 100 μL (1000 ng · mL^{-1}) of internal standard and 1.5 mL of methyl tert-butyl ether (J.T. Baker México, Xalostoc, Mexico) were added. The samples were then mixed on a vortex mixer (FINEPCR, Gunpo, South Korea) and centrifuged (JOUAN SA) at 10,000 rpm for 5 minutes at 4°C. After separation, the organic phase was transferred to 2-mL glass vials, and the solvent was evaporated to dryness at 40°C under a nitrogen stream (White Martins Gases Industrias Ltda., Rio de Janeiro, Brazil). The residue was redissolved in 200 μL of mobile phase, and 200 μL was transferred to 250-μL glass vials and placed in an autosampler (Shimadzu Corporation, Tokyo, Japan) for analysis.

HPLC-MS/MS Conditions

HPLC was performed using an SCL-10AVP chromatography system fitted with an LC-10ADvp quaternary pump, DGU-14A degasser, and SIL-10ADvp autosampler (Shimadzu Corporation). Chromatographic separation was performed on an ACE C8 column (50 × 4.6 mm, 5 μm; Advanced Chromatography Technologies, Aberdeen, United Kingdom) at a column temperature of 40°C. The mobile phase used for isocratic elution consisted of 20 mM of ammonium acetate buffer (Acros Organics, Geel, Belgium) and acetonitrile (20:80 v/v), which was filtered using 0.45-μm filters in a Millipore solvent filtration apparatus (Millipore Corporation, Billerica, Massachusetts). The flow rate was 1.50 mL/min, and the postcolumn splitting ratio was 10:1. The injection volume was 20 μL, and the analysis time was 1.5 minutes per sample.

The compounds were ionized by electrospray ionization with the mass spectrometer (Micromass Quattro LC, Waters Corporation, Milford, Massachusetts) operated in the positive-ion mode. The multiple reaction monitoring mode was used for quantitation by the ion transition of analyte (277.90 > 260.03) and internal standard (309.80 > 147.78). The detection conditions were as follows: capillary voltage, 3.20 kV; cone voltage, 23 V for venlafaxine and 20 V for internal standard; extractor voltage, 2.0V for venlafaxine and fluoxetine; source temperature, 120°C; desolvation temperature, 350°C; and desolvation gas flow, 400 L/h.

The method was validated according to ANVISA,[15] Good Laboratory Practice,[16] and FDA guidelines.[17] Recovery, linearity, lower limit of quantitation, precision, accuracy, specificity, and stability were determined.

Pharmacokinetic and Statistical Analysis

Venlafaxine plasma concentrations were analyzed as a function of time. The following pharmacokinetic parameters were obtained for each formulation: C_{max}, T_{max}, AUC_{0-t} (where t was the last time point at which concentrations were measurable), and $AUC_{0-\infty}$. C_{max} and T_{max} were obtained directly from the original data set, and AUC_{0-t} was calculated using the linear trapezoidal rule. $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/k_e$, where C_t was the last measured concentration and k_e (elimination rate constant) was calculated using linear regression analysis of the log-linear portion of the plasma concentration–time curve. The $t_{1/2}$ was calculated as $\ln_2/k_e$.[18,19]

Values for T_{max} were compared using the Wilcoxon rank sum test.[20] Applying a noncompartmental model to the log-transformed data, venlafaxine C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were compared by ANOVA for a crossover design, taking into account the effects of formulation, period, sequence, and subject.[20–22]

The Schuirmann[21] and Anderson-Hauck[23] tests were used to examine bioequivalence. The ratios and 90% CIs of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were calculated for both formulations, and 2 one-sided t tests were used to evaluate whether the 90% CIs of the geometric mean ratios (test:reference) for these parameters met the ANVISA[13] and FDA[14] criterion for bioequivalence (ie, were within the 80%–125% range).

All pharmacokinetic and statistical analyses were performed using WinNonlin Professional Software version 5.1 (Pharsight Corporation, Mountain View, California). Differences were considered statistically significant at $P < 0.05$.

Because no published data were found regarding the sample size to be used in bioequivalence testing of venlafaxine products and because venlafaxine is associated with a number of adverse effects that might lead to study discontinuation, it was decided to employ a sample size of 48 volunteers to ensure >80% statistical power.

RESULTS

Subjects

Forty-eight subjects were enrolled in both phases of the study. All 48 subjects completed the fasting phase. Ten subjects withdrew before the beginning of the fed phase and were replaced by new subjects. One subject withdrew during the fed phase, which was completed by all 47 remaining subjects. There were no

significant differences in the age, weight, or height of volunteers in the fasting and fed portions of the study (**Table I**).

Tolerability

The test and reference formulations were well tolerated in both the fasting and fed portions of the study. AEs were reported in 58% and 28% of subjects, respectively. The most common AEs (≥5% of subjects) in the fasting phase were nausea (46%), headache (29%), diarrhea (29%), vomiting (15%), and colic (6%); the most common AEs in the fed phase were nausea (15%), headache (13%), and dizziness (9%) (**Table II**).

Method Validation

The mean (SD) extraction recovery of venlafaxine, as determined at 3, 30, and 60 ng/mL, was 75.48% (3.68%), 61.67% (7.78%), and 59.86% (27.47%), respectively, while that of internal standard at 1000 ng/mL was 74.74% (10.2%). The lower limit of quantitation for venlafaxine in 0.4 mL of human plasma was 1 ng/mL. Linearity was achieved over a concentration range from 1 to 70 ng/mL, with a typical equation for the calibration curve of $y = 0.0330811x + 0.0360921$ ($r > 0.986756$). Intraday and interday accuracy were 89.02% to 106.42% and 96.18% to 100.35%, respectively; intraday and interday precision were 4.94% to 14.15% and 7.31% to 11.05%.

Pharmacokinetic and Statistical Parameters

The mean venlafaxine plasma concentration–time profiles under fasting and fed conditions are shown in the **figure**. In the fasting phase, the arithmetic mean (SD) C_{max} for the test and reference formulations was 35.705 (23.946) and 34.470 (20.639) ng/mL, respectively, with a geometric mean ratio of 1.04 (**Table III**). The arithmetic mean AUC_{0-t} for the respective formulations was 562.015 (481.875) and 508.509 (439.456) ng · h/mL, with a geometric mean ratio of 1.11.The arithmetic mean $t_{1/2}$ was 8.808 (2.610) and 8.960 (2.566) hours. The arithmetic mean T_{max} was 6.188 (1.560) and 5.885 (1.648) hours. Based on the nonparametric Wilcoxon test, there was no significant difference in T_{max} between the 2 formulations.

In the fed phase, the arithmetic mean (SD) C_{max} for the test and reference formulations was 42.892 (24.348) and 46.275 (23.011) ng/mL, respectively, with a geometric mean ratio of 0.93 (**Table III**). The arithmetic mean AUC_{0-t} for the respective formulations was 737.218 (603.998) and 682.124 (524.713) ng · h/mL, with a geometric mean ratio of 1.08. The arithmetic mean $t_{1/2}$ was 8.319 (2.682) and 8.327 (3.292) hours. The arithmetic mean T_{max} was 6.787 (1.769) and 5.957 (1.661) hours. Based on the nonparametric Wilcoxon test, there was no significant difference in T_{max} between the 2 formulations.

Table I. Age, weight, and height data for healthy Brazilian male volunteers participating in the fasting and fed phases.

Variable	Fasting (n = 48)	Fed (n = 47)
Age, y		
Mean (SD)	24.96 (5.5)	24.90 (4.7)
%CV	21.9	18.7
Range	18–44	18–43
Weight, kg		
Mean (SD)	69.65 (9.6)	71.00 (10.6)
%CV	13.9	15.0
Range	50–89	50–93
Height, cm		
Mean (SD)	172.00 (6.9)	173.00 (6.6)
%CV	4.0	3.8
Range	157–190	159–189

Table II. Summary of adverse events (AEs) in the fasting and fed phases.

AE	Fasting (n = 48)	Fed (n = 47)
No. (%) of patients with AEs	28 (58)	13 (28)
Individual AEs, no. (%)		
Nausea	22 (46)	7 (15)
Headache	14 (29)	6 (13)
Diarrhea	14 (29)	2 (4)
Vomiting	7 (15)	1 (2)
Colic	3 (6)	1 (2)
Hypertension	1 (2)	–
Insomnia	1 (2)	–
Dizziness	–	4 (9)
Somnolence	–	1 (2)

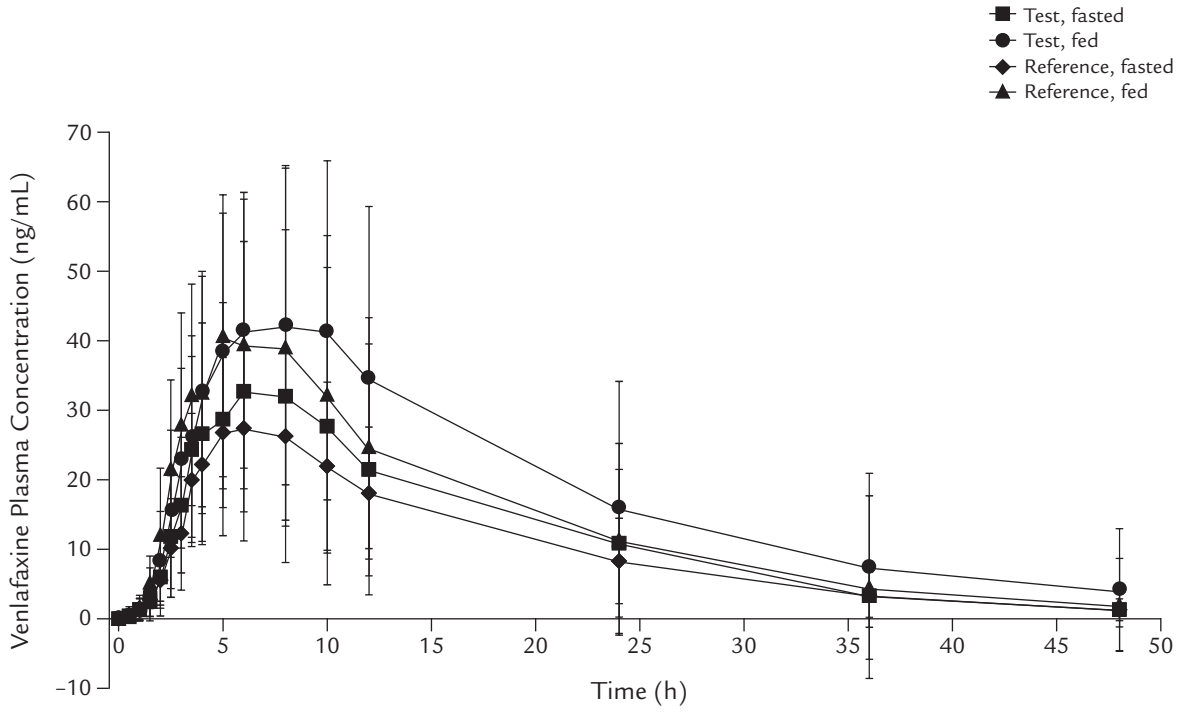

Figure. Mean (SD) venlafaxine concentration–time profiles after administration of single oral doses of the test (manufactured by Cristália Produtos Químicos Farmacêuticos Ltda., Itapira, São Paulo, Brazil) and reference (Effexor XR®; Wyeth Pharmaceuticals Company, Inc., Guayama, Puerto Rico) formulations of venlafaxine extended-release 75-mg capsules.

Table III. Arithmetic mean (SD) pharmacokinetic parameters of venlafaxine after oral administration of single doses of the test* and reference† formulations of venlafaxine extended-release 75-mg capsules in the fasting (n = 48) and fed (n = 47) phases.

	Test		Reference	
Parameter	Fasting	Fed	Fasting	Fed
C_{max}, ng/mL	35.705 (23.946)	42.892 (24.348)	34.470 (20.639)	46.275 (23.011)
AUC_{0-t}, ng · h/mL	562.015 (481.875)	737.218 (603.998)	508.509 (439.456)	682.124 (524.713)
$AUC_{0-\infty}$, ng · h/mL	608.051 (492.397)	805.728 (747.720)	560.981 (508.232)	741.382 (649.850)
T_{max}, h	6.188 (1.560)	6.787 (1.769)	5.885 (1.648)	5.957 (1.661)
λ_z, h^{-1}	0.084 (0.020)	0.090 (0.023)	0.084 (0.026)	0.092 (0.025)
$t_{1/2}$, h	8.808 (2.610)	8.319 (2.682)	8.960 (2.566)	8.327 (3.292)

λ_z = terminal elimination rate constant.
*Manufactured by Cristália Produtos Químicos Farmacêuticos Ltda., Itapira, São Paulo, Brazil.
†Trademark: Effexor XR® (Wyeth Pharmaceuticals Company, Inc., Guayama, Puerto Rico).

The results of statistical comparisons between formulations in the fasting and fed portions of the study are summarized in **Table IV**.

Relative Bioavailability

In the fasting phase, the 90% CIs for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 93.24 to 105.93, 102.90 to 116.71, and 101.72 to 115.26, respectively. In the fed phase, the corresponding values were 84.67 to 97.85, 98.19 to 114.41, and 98.23 to 114.36. Thus, the 90% CIs for these parameters in both phases of the study were within the acceptance range for bioequivalence.

DISCUSSION

According to ANVISA[13], the FDA,[14] and the World Health Organization (WHO),[24] relative bioavailability studies of orally administered modified-release products are to be performed under both fasting and fed conditions. Relative bioavailability studies conducted in the fed state are intended to compare the bioavailability of the test and reference products when administered with meals. In the present study under fasting and fed conditions, the 90% CIs for the ratios of mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the ANVISA acceptance range of 80% to 125%.[13] Under both fasting and fed conditions, the T_{max} of the test formulation occurred later than that of the reference formulation. The differences were not statistically significant and are not likely to be clinically relevant; according to WHO guidelines on registration requirements for the establishment of interchangeability, statistical evaluation of T_{max} "only makes sense if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects."[24]

The difference in pharmacokinetic parameters between the fasting and fed phases was tested statistically using ANOVA. In the case of the test formulation, no significant differences in pharmacokinetic parameters were found between the fasting and fed portions of the study (calculated value of the *F* distribution [F_{calc}] less than the critical value of the *F* distribution [F_{critic}]). In the case of the reference formulation, no significant differences in AUC_{0-t} or $AUC_{0-\infty}$ were found between the fasting and fed portions of the study, although there was a significant difference in C_{max} ($F_{calc} > F_{critic}$; $P < 0.05$). On ANOVA, there were no significant differences with regard to the effects of formulation, period, sequence, or subject nested in sequence in the fasting and fed portions of the study. The fact that no significant sequence effect was observed in either the fasting or fed portion of the study indicates that the washout period was appropriate and that no carryover effect was present.

Certain aspects of the study design, although consistent with regulatory guidelines (eg, the single-dose, open-label design and population of healthy volunteers), limit the generalizability of the results beyond the population and conditions studied.

CONCLUSION

In this single-dose study conducted under fasting and fed conditions in healthy male volunteers, the test and reference extended-release venlafaxine 75-mg capsules were found to meet Brazilian criteria for acceptance of bioequivalence.

Table IV. Results of statistical comparisons between the test* and reference† formulations of venlafaxine extended-release 75-mg capsules in the fasting and fed phases (ANOVA; $P < 0.05$).

	C_{max}		AUC_{0-t}		$AUC_{0-\infty}$	
Variable	Test	Reference	Test	Reference	Test	Reference
Geometric mean ratio	0.832	0.740	0.763	0.745	0.755	0.755
F_{calc}	2.104	6.936	2.448	3.062	2.280	2.332
F_{critic}	3.943	3.943	3.943	3.943	3.943	3.943

F_{calc} = calculated value of the *F* distribution; F_{critic} = critical value of the *F* distribution.
* Manufactured by Cristália Produtos Químicos Farmacêuticos Ltda., Itapira, São Paulo, Brazil.
† Trademark: Effexor XR® (Wyeth Pharmaceuticals Company, Inc., Guayama, Puerto Rico).

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Mr. de Souza Filho, Mr. Sardón, Ms. Gonçalves, and Dr. Leal were responsible for the planning and execution of the clinical phase of the study, and Dr. de Santana was the coordinator for NUDFAC. Dr. Bonifácio, Mr. Bedor, and Mr. Miranda de Sousa were responsible for development and validation of the analytic method and analysis of the data; and Ms. Ramos was responsible for the statistical analysis. Dr. Moreira was responsible for final revision of the article. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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