ISSN: 0975-0851
Journal of Bioequivalence & Bioavailability

OPEN ACCESS Freely available online

Research Article

Levetiracetam Coated Tablet: A Randomized, Single-Dose, Two-Sequence, Two-Period, Crossover Study to Assess the Bioequivalence between Two Formulations

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ABSTRACT

Levetiracetam is an antiseizure medication prescribed to treat epilepsy. This study aimed to evaluate the bioequivalence between two formulations of levetiracetam coated tablets in order to meet regulatory requirements for marketing in Brazil. An open-label, randomized, single-dose, two-period, two-sequence, two-treatment crossover study was conducted in Brazilian healthy subjects of both genders. Subjects received a single dose of Levetiracetam 1000 mg test tablet (Zodiac Produtos Farmacêuticos S.A) and reference product (Etira®, Aché Laboratórios Farmacêuticos S.A.) under fasting conditions according to a randomly assigned order with a 7-day washout period. Serial blood samples were collected up to 36 h post-dose. Plasma concentrations of levetiracetam were obtained by a validated liquid chromatography-tandem mass spectrometry method. Pharmacokinetic parameters were calculated using non-compartmental methods. A total of 32 healthy subjects were enrolled and 31 subjects completed the study. There were no serious adverse events during the study. Geometric mean ratios (90% confidence intervals) for C_{max}, AUC_{0-t} and AUC_{0-inf} were 99.06% (90.61%-108.28%), 101.57% (99.75%-103.42%) and 101.02% (98.90%-103.18%), respectively. The test formulation of levetiracetam 1000 mg coated tablet (Zodiac Produtos Farmacêuticos S.A.) was considered bioequivalent to reference product Etira® (Aché Laboratórios Farmacêuticos S.A.) according to regulatory requirements. Both formulations were safe and well tolerated during the study. Levetiracetam 500 mg strength was waived of *in vivo* testing based on proportional similarity of the formulations and similar *in vitro* dissolution profiles between the strengths.

Keywords: Levetiracetam; Epilepsy; Bioequivalence; Pharmacokinetics; Bioavailability; Bioanalytical method

INTRODUCTION

Levetiracetam (second generation anticonvulsant) is an antiseizure medication indicated as mono-therapy for the treatment of focal onset seizures, with or without secondarily generalized in patients 16 years of age and older with recent diagnosis of epilepsy. It is also indicated as adjuvant therapy for the treatment of focal seizures with or without secondarily generalized in adults, adolescents and children over 6 years of age (weight ≥ 25 kg) with epilepsy. In Brazil, this drug is also indicated for two more conditions:

1. Myoclonic seizures in adults, adolescents and children over 12 years of age with juvenile myoclonic epilepsy.
2. Generalized primary tonic-clonic seizures in adults, adolescents and children over 6 years of age (weight ≥ 25 kg), with generalized idiopathic epilepsy [1].

Levetiracetam is an (S)-enantiomer of the ethyl analog of piracetam and its mechanism of action is not yet completely known. However, in animal models, it has been observed that the drug binds to a synaptic vesicle protein, SV2A, which has been related to modulation of synaptic vesicle exocytosis and neurotransmitter release [2,3].

Levetiracetam is a highly soluble and permeable drug (BCS class I) [4]. After oral administration, the drug is rapidly and almost completely absorbed (96%) and the plasma concentrations increase proportionally to dose over the therapeutic range (250 mg-5000 mg). Maximum plasma concentrations of levetiracetam are reached approximately 1.1 h (T_{max}) after tablet administration and the absorption is equally efficient taken as a single dose or in multiple doses [1,5]. It is not highly plasma protein-bound (<10%) and not extensive metabolized in humans. Biotransformation occurs mainly

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Received: 25-Feb-2022, Manuscript No. JBB-22-15705; **Editor assigned:** 28-Feb-2022, PreQC No. JBB-22-15705 (PQ); **Reviewed:** 14-Mar-2022, QC No. JBB-22-15705; **Revised:** 21-Mar-2022, Manuscript No. JBB-22-15705 (R); **Published:** 28-Mar-2022, DOI:10.35248/0975-0851.22.14.458

Citation: Davanço MG, Meulman J, Costa F, Teixeira LS, Mundim IM, Bellorio KB, et al. (2022) Levetiracetam Coated Tablet: A Randomized, Single-Dose, Two-Sequence, Two-Period, Crossover Study to Assess the Bioequivalence between Two Formulations. J Bioequiv Availab. 14:458.

by enzymatic hydrolysis (24% of dose) of the acetamide group, and the main metabolite is pharmacologically inactive. Levetiracetam half-life ($T_{1/2}$) is approximately 7 h in plasma. There is no evidence of accumulation during multiple administrations [1].

Generic products must present the same efficacy and safety (therapeutically equivalent) as of the reference products in order to be interchangeable with it. The comparison between a test formulation (generic candidate) and its respective reference formulation could be performed through pharmacokinetic profiles and bioequivalence assessment. This approach aims to guarantee that both drug formulations present the same rate and extent of absorption [6].

This study assessed the bioequivalence and tolerability of two formulations of levetiracetam 1000 mg coated tablet. The test formulation was manufactured by Monte Verde S.A. (San Juan, Argentina) and imported to Brazil by Zodiac Produtos Farmacêuticos S.A. (Pindamonhangaba, São Paulo, Brazil). The reference formulation, trade name Etira® , was manufactured by Aché Laboratórios Farmacêuticos S.A. (Guarulhos, São Paulo, Brazil). All tests were performed in order to attend the regulatory requirements from ANVISA (Brazil) for bioequivalence studies and to certify that the generic formulation (Zodiac Produtos Farmacêuticos S.A.) is bioequivalent to the reference product (Etira®) [6].

MATERIALS AND METHODS

Ethical approval and good clinical practices

This study was approved by the Research Ethics Committee of the Instituto de Ciências Farmacêuticas de Estudos e Pesquisas (Aparecida de Goiânia, Goiás, Brazil) with protocol number 3.778.989. The clinical, analytical and statistical phases were performed at the Instituto de Ciências Farmacêuticas de Estudos e Pesquisas (Goiânia, Goiás, Brazil), a Brazilian CRO certified by ANVISA to conduct bioequivalence studies.

This study followed the Good Clinical Practices Guidelines, the ethical principles for medical research involving human subjects stated in the Declaration of Helsinki, Resolution n. 466/2012 (Ministério da Saúde, Brazil) and ANVISA (Brazil) requirements for bioequivalence studies [6-9]. Informed consent was obtained from all participants prior to initiation of study procedures.

Subjects and study design

Thirty-two (32) adult healthy subjects of both genders (16 male and 16 non-pregnant female subjects) were enrolled in the study. The sample size was determined by taking into account published data of intra-subject variability of drug (coefficient of variation within-subject of C_{max}). The subjects had not previously participated in another clinical trial nor donated blood during the preceding six months and had no history of alcohol or drug abuse. They were aged between 18 and 50 years with a body mass index between 18.5 kg/m^2 and 24.9 kg/m^2. All subjects showed good health conditions or the absence of significant diseases after assessment of medical history, verification of vital signs, physical examination, electrocardiogram and routine laboratory tests. The study design was randomized, single dose, fasting, two-period, two-sequence crossover with a 7-day washout period.

Products studied

Test product: Levetiracetam 1000 mg coated tablet (batch No. 84947, expiry date: May 2021). The test product was manufactured by Monte Verde S.A. (San Juan, Argentina) and imported to Brazil by Zodiac Produtos Farmacêuticos S.A. (Pindamonhangaba, São Paulo, Brazil).

Reference product: Etira® 1000 mg coated tablet (batch No. 1910563, expiry date: August 2021). The reference product was manufactured by Aché Laboratórios Farmacêuticos S.A. (Guarulhos, São Paulo, Brazil).

Drug administration and sample collection

In each period, after a minimum overnight fasting of 8 hours, the subjects received a tablet containing 1000 mg of levetiracetam from one of the two formulations as a single dose with 200 mL of water. They were maintained fasted for 4 h after drug administration and water was not allowed during the 2 h before and after drug administration. In order to maintain the standardization of treatment groups, the diet (food and drink) followed the same standard for all subjects and in both periods. The intake of alcoholic beverages, food or beverages containing caffeine or xanthine (such as coffee, tea, chocolate and cola or guarana-based soft drinks) was not allowed.

A total of 21 blood samples were collected at 0 h (before drug administration) and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.17, 1.33, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0 and 36.0 h (after drug administration) in tubes containing sodium heparin as anticoagulant at each time point. Collected blood samples were centrifuged immediately (3,000 rpm for 5 min at 4°C); plasma was separated and stored frozen at -20 °C with appropriate labeling until sample analysis.

Sample analysis

Plasma concentrations of levetiracetam were determined using high performance liquid chromatography with sequential mass spectrometry (HPLC Agilent 1200 series coupled to Sciex API 3200 MS/MS). Cimetidine hydrochloride was used as an internal standard. The analytes were extracted from plasma by protein precipitation. In order to avoid inter-assay variations, all samples from the same volunteer were assessed in the same analytical run. The chromatographic analysis was conducted with a column Inertsil ODS-4 (4.6 × 100 mm, 5 µm) and flow rate of 1.4 mL/min. The column was maintained at 25°C and the auto-sampler at 20°C. The mobile phase used was a solution of 0.025% formic acid with 2 mM ammonium acetate; and methanol at a 55:45 ratio (v/v). The injection volume was 5 µL and the total run time set as 2 min. The mass spectrometry detection was conducted using electrospray ionization source in positive mode. The Multiple Reaction Monitoring (MRM) method was used, and the transitions monitored were m/z 171.12>126.00 and m/z 253.12>159.20 for levetiracetam and cimetidine, respectively. The bioanalytical method was validated in compliance with ANVISA guidance for bioanalytical method validation [10]. The validation parameters previously assessed were selectivity, linearity, intra and inter-run precision, intra and inter-run accuracy, matrix effect, residual effect (carryover), and stability of levetiracetam under different conditions.

Safety

In this study, all the subjects were continuously and carefully monitored. Safety was assessed by monitoring vital signs (temperature, blood pressure, heart rate, and respiratory rate) at baseline before dosing and during the study. Laboratory

tests (hematology, urinalysis, and blood biochemistry), physical examinations, and ECGs were also performed at baseline and at completion of the study. Adverse events were assessed at the time of each blood draw using direct observation, spontaneous reporting, and nonspecific questioning. Any undesirable sign, symptom, or medical condition occurring after the start of the study was recorded regardless of the suspected relationship to the drug studied. Adverse events were graded as mild, moderate, or intense, and their relationship to the study drug was determined by the study physicians as not related, unlikely related, uncertain, possibly related, probably related, or definitely related.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters were obtained from the curves of plasma concentration versus time for levetiracetam and statistically compared for determination of bioequivalence, using Phoenix WinNonLin software version 6.0 (Bioequivalence Wizard module). The area under the curve from zero to the last quantifiable concentration (AUC_{0-t}) was calculated by the trapezoidal method, and the area under the curve from zero to infinity (AUC_{0-inf}) was calculated by the formula AUC_{0-t}+(Cn/kel), where Cn was the last quantifiable plasma concentration. The elimination constant (kel) was determined by elimination phase of the graph of log plasma concentration versus time. The $t_{1/2}$ was defined using the equation $t_{1/2}$=Ln(2)/kel. The maximum plasma drug concentration (C_{max}) was obtained directly from the experimental data, as well as the time of the occurrence of C_{max} (t_{max}).

Bioequivalence assessment was based on predefined acceptance criteria of 80.00%-125.00% for the 90% confidence interval for the ratio of the test and reference products for the log-transformed data of AUC and C_{max}, as recommended by ANVISA [6]. An ANOVA test was performed for the primary parameters estimated (C_{max} and AUC) to evaluate formulation, sequence, and period as fixed effects.

RESULTS AND DISCUSSION

Subjects and safety

Thirty-two subjects were enrolled in the study and thirty-one (16 women and 15 men) completed the two study periods. One subject was excluded due to chocolate containing alcohol intake. The average age was 33.23 years (20 to 45 years old). Average weight was 69.37 Kg (50.00 Kg to 90.00 Kg). Average height was 1.68 m (1.47 m to 1.85 m) and average BMI was 24.46 Kg/m^2 (18.86 Kg/m^2 to 28.61 Kg/m^2). A total of 35 adverse events were reported by 15 subjects since the beginning of the confinement until the post-study period. The most common adverse events were dizziness and headache, reported by 53% and 46% of subjects, respectively. These events were reported for both treatments (Test and Reference) and are considered common (dizziness) and very common (headache) events as reported on the prescribing information. All adverse events reported were considered as mild. 25 adverse events were classified as causality possibly related to the drug and 10 of them were considered causality not related to the drug. No serious adverse event was observed or reported.

Sample bioanalysis

The validated method covered all required tests, including evaluation of the carry-over effect, selectivity, matrix effect, linearity, accuracy, precision and stability. Levetiracetam (parent drug) and cimetidine (IS) were extracted from human plasma by protein precipitation.

The selectivity of the method was proved to be adequate by showing that substances in the plasma blank did not interfere at the retention times of levetiracetam and IS. The relationship between concentration and peak area ratio was found to be linear within the range from 200 ng/mL to 40,000 ng/mL for levetiracetam. The intra-day accuracy of the method for levetiracetam ranged from 87.9% to 105.7%, while the intraday precision ranged from 0.7% to 4.6%. The inter-day accuracy ranged from 90.6% to 98.7%, while the inter-day precision ranged from 2.1% to 6.9%.

The levetiracetam stability assay showed that the drug in the final extract was stable for 44.5 h at room temperature (15°C to 25°C), stable in plasma at room temperature (15°C to 25°C) for 6.33 h, stable after three freeze-thaw cycles at -20°C and -80°C, and stable when frozen at -20°C and -80°C for 34 days. These tests are of fundamental importance for the samples to be properly stored until the analysis, ensuring the determination of reliable drug concentrations.

Levetiracetam was not detected in plasma samples of any participant in the pre-dose sample indicating the absence of carryover effects and ensuring an adequate washout period.

Finally, all validation parameters met the predefined acceptance criteria according to ANVISA bioanalytical method validation guideline [10].

Pharmacokinetic parameters

In order to verify whether the test product would be bioequivalent to the reference product when administered under fasting condition, the present study was planned and performed as an open, randomized, single-dose, crossover (two-treatments, two-sequences and two-periods) study, balanced between gender (healthy subjects) and with washout of 7-days between the periods.

Figure 1 shows the mean plasma concentration–time curves for levetiracetam administration of the test and reference products. The pharmacokinetic parameters of levetiracetam for both products are described in Table 1.

Table 1: Pharmacokinetic parameters of levetiracetam tablets administered under fasting condition in healthy subjects (mean ± standard error, N=31).

Parameter	Test	Reference
C_{max} (ng/mL)	30,827.5 ± 7,665.7	31,141.2 ± 7,595.8
AUC_{0t} (ng/mL • h)	256,839.3 ± 47,430.8	252,900.3 ± 46,294.3
AUC_{0inf} (ng/mL • h)	265,814.2 ± 49,399.1	263,007.7 ± 47,559.5
t_{max} (h)	0.97 ± 0.83	1.12 ± 0.93
$t_{1/2}$ (h)	7.33 ± 0.86	7.33 ± 0.99
kel (1/h)	0.096 ± 0.012	0.096 ± 0.013

Note: C_{max}: Maximum plasma concentration; t_{max}: Time to reach C_{max}; AUC_{0t}: Area under the concentration-time curve from zero to 36 h; AUC_{0inf}: Area under the concentration-time curve extrapolated to infinity; $t_{1/2}$: Elimination half-life; kel: Elimination constant.

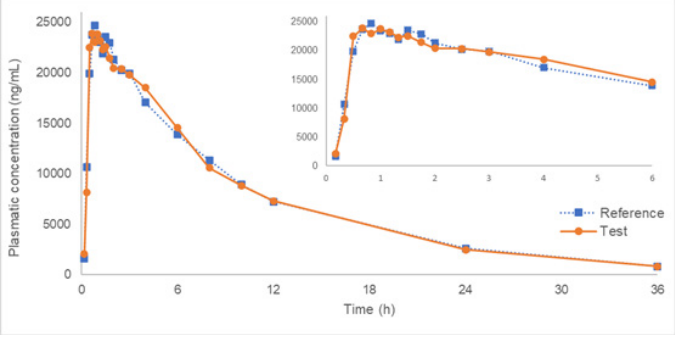

Figure 1: Mean levetiracetam plasma concentrations vs. time profiles after administration of test and reference products. A, concentration-time curve from zero to 36 h. B, concentration-time curve focused on the range from zero to 6 h (N=31, healthy subjects).

In Figure 1, it was possible to observe that the pharmacokinetic profile of levetiracetam was very close between formulations. Moreover, the sampling time can be considered adequate, since it was possible to describe correctly the absorption and elimination phases in the levetiracetam oral tablet administration.

Considering the mean pharmacokinetic parameters presented in Table 1, it was possible to observe that C_{max} (test 30,827.5 ± 7,665.7 ng/mL and reference 31,141.2 ± 7,595.8 ng/mL) and t_{max} (test 0.97 ± 0.83 h and reference 1.12 ± 0.93 h), parameters related to rate of absorption, are similar to other published studies. For example, Zava (2019), in a bioequivalence study conducted in healthy subjects, showed C_{max} and t_{max} of 31,893 ng/mL and 0.75 h, respectively, for test product; and C_{max} and t_{max} of 30,510 ng/mL and 0.83 h, respectively, for reference product [11].

Boudriau and collaborators (2016), in a comparative bioavailability study, demonstrated C_{max} of 30,480 ng/mL and T_{max} of 0.58 h after oral administration of levetiracetam 1000 mg conventional immediate-release tablet under fasted condition [12].

Vespasiano and collaborators (2019), in a bioequivalence study between two formulations of levetiracetam 750 mg coated tablet, found C_{max} of 21,299 ± 801.9 ng/mL, AUC_{0-t} of 187,450.7 ng/mL × h and T_{max} of 0.81 h (0.33 h-2.00 h) for the test product; and C_{max} of 21,910 ± 842.9 ng/mL, AUC0-t of 188,845.6 ng/mL × h and T_{max} of 1.00 h (0.33 h-6 h) for the reference product. These C_{max} and AUC_{0-t} results of 750 mg tablet could be considered proportionally similar to our results with 1000 mg tablet. Additionally, in terms of T_{max}, the different strengths (750 mg vs. 1000 mg) also demonstrate very close absorption rates [13].

Regarding to parameter $t_{1/2}$, the data obtained in our study were also very close to other published ones. Levetiracetam administered as both test and reference products present $t_{1/2}$ of 7.33 h. This data is in accordance with the results published by Zava (Test $t_{1/2}$=7.43 h and Reference $t_{1/2}$=7.64), Boudriau and collaborators ($t_{1/2}$=7.14 h), and Vespasiano and collaborators (Test $t_{1/2}$=7.48 h and Reference $t_{1/2}$=7.68) [11-13].

Table 2 presents the test/reference geometric mean ratios for pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} and the respective 90% CIs for the bioequivalence analysis.

Table 2: Geometric mean ratio, confidence intervals (90%), power and CVws.

Parameter*	Geometric mean ratio %	90% CI	Power %	CVws %
C_{max}	99.06	90.61-108.28	98.66	20.85
AUC_{0-t}	101.57	99.75-103.42	100	4.19
AUC_{0-inf}	101.02	98.90-103.18	100	4.9

Note: *Parameters logarithmically Ln-transformed; C_{max}: Maximum plasma concentration; AUC_{0-t}: Area under the concentration-time curve from 0 to 36 h; AUC_{0-inf}: Area under the concentration-time curve extrapolated to infinity; CI: Confidence Interval; CVws: Coefficient of Variation within subject.

A non-compartmental model was used for the analysis of pharmacokinetic parameters presented in Table 2. The comparative bioequivalence between the two products were estimated by the analysis of variance (ANOVA) for two-way crossover design. There were no significant effects of formulation, sequence and period on this study. The 90% CI of logarithmically Ln-transformed of the ratios (Test/Reference) of C_{max}, AUC_{0-t} and AUC_{0-inf} were 90.61%-108.28%, 99.75%-103.42% and 98.90%-103.18%, respectively, which were within the acceptable range of 80.00-125.00% established by ANVISA. Therefore, it was concluded that generic levetiracetam 1000 mg coated tablet, registered in Brazil by Zodiac Produtos Farmacêuticos S.A. (test formulation), and Etira® 1000 mg coated tablet (reference formulation) were bioequivalent in terms of rate and extent of absorption. As described in FDA product-specific guidance and ANVISA requirements, levetiracetam 500 mg strength was waived of *in vivo* testing based on acceptable bioequivalence study on the 1000 mg strength, proportional similarity of the formulations across all strengths, similar *in vitro* dissolution profiles of all strengths (data not shown) and levetiracetam linear pharmacokinetics (250 mg-5000 mg) [14].

Figures 2 and 3 shows the dispersion of test/reference ratio for C_{max} and AUC_{0-t}, respectively between the subjects who concluded the study.

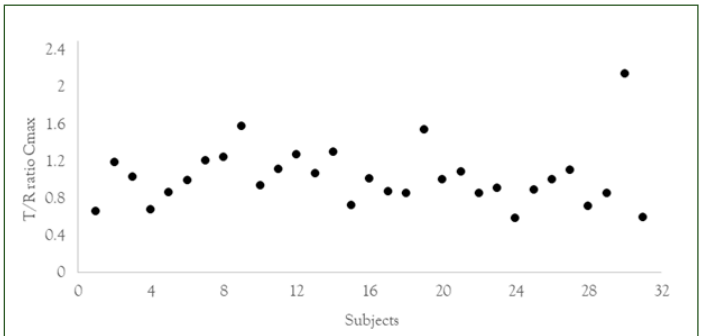

Figure 2: Dispersion of results for test/reference ratio for C_{max} between the subjects (N=31).

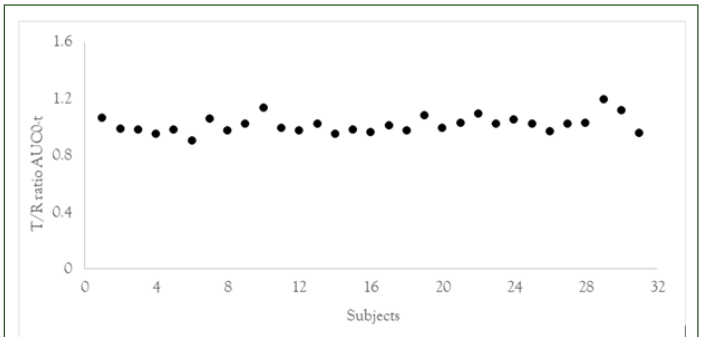

Figure 3: Dispersion of results for test/reference ratio for AUC_{0-t} between the subjects (N=31).

Figures 2 and 3 demonstrated the low intra-subject variability between test and reference for ratios of C_{max} and AUC_{0-t}. It also can be observed through CV within subject data (Table 2), 20.85% for C_{max} and 4.19% for AUC_{0-t}. Therefore, levetiracetam can be considered a low-variability drug (*in vivo*) and to calculate the

sample size for bioequivalence studies is necessary to consider the parameter C_{max} (worst scenario to variability within subject)

CONCLUSION

Based on 90% CI for the ratio of geometric means (test/reference) of logarithmically transformed C_{max}, AUC_{0-t} and AUC_{0-inf}, the conclusion of bioequivalence can be made for the two formulations of levetiracetam 1000 mg coated tablet (test and reference). According to study data, it can be confirmed that drug exposure between the reference and test formulations is equivalent. Both formulations were well tolerated and no relevant differences in safety profiles between them were found. In conclusion, considering that the bioavailability of the test and reference formulations is essentially similar as well as the safety data observed in this study, the levetiracetam generic formulation (all strengths) registered in Brazil by Zodiac Produtos Farmacêuticos S.A. is considered bioequivalent to the reference formulation (Etira®) and is expected to produce the same therapeutic response. Thus, these products may be considered as being interchangeable in medical practice, i.e., having the same efficacy and safety profile.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article. The authors were fully responsible for all content and editorial decisions and did not receive financial support from Zodiac or any other form of compensation related to the development of this article.

ACKNOWLEDGMENTS

The authors thank the ICF (Brazil) team for technical support in Clinical, Analytical and Statistical phases of the bioequivalence study; and Monte Verde (Argentina) team for the generic formulation development.

FUNDING DETAILS

The bioequivalence study was financially supported by Zodiac Produtos Farmaceuticos S.A.

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