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Bioequivalence of two formulations of 750 mg levetiracetam extended-release coated tablets in healthy volunteers under fasting and fed conditions

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Abstract

Objective: To evaluate the bioequivalence of the two formulations of Eurofarma's Levetiracetam 750 mg Extended Release Coated Tablets (Test Product [T]) against Keppra XR (Reference Product [R]) in healthy adults under fasting and fed conditions. **Methods:** The studies were designed as open, randomized, balanced, two treatments, two-period, single dose, crossover under fasting and fed condition with seven days washout interval. The assigned subjects were given test tablets and reference tablets in each period orally at a dose of 750 mg under fasting and fed conditions. Each study involved 32 subjects. In both the studies under fasting and fed conditions, the major pharmacokinetic parameters were calculated by SAS® Software 9.4 and the bioequivalence was evaluated. **Results:** For bioequivalence evaluation a total of 31 subjects completed the fasting study, and 29 subjects completed the fed study. The 90% confidence intervals for the geometric mean ratios of Levetiracetam area under the curve (AUC_{0-T} and $AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) were within the established bioequivalence limits of 80% to 125%. A total of three adverse events were reported during the conduct of the two studies, with one event possibly related to the study medication and the other two considered unrelated. All adverse events were mild to moderate in severity and did not significantly impact the participants' quality of life. No serious adverse events were reported. **Conclusion:** It can be concluded that the two formulations can be used interchangeably

Keywords: antiepileptic, levetiracetam, LC/MS-MS, bioequivalence, pharmacokinetics

Bioequivalência entre duas formulações de comprimidos revestidos de liberação prolongada de levetiracetam 750 mg em voluntários saudáveis nas condições de jejum e alimentado

Resumo

Objetivo: Avaliar a bioequivalência de duas formulações de Levetiracetam 750 mg Comprimidos de Liberação Prolongada revestidos da Eurofarma (Produto Teste [T]) em comparação com Keppra XR (Produto de Referência [R]) em adultos saudáveis, nos estados de jejum e alimentado. **Métodos:** Foram conduzidos ensaios abertos, randomizados, balanceados, com dois tratamentos, dois períodos e dose única, em desenho cruzado (crossover), nos estados de jejum e alimentado, com período de *washout* de sete dias. Os voluntários receberam os comprimidos teste e referência em cada período, por via oral, na dose de 750 mg, tanto em jejum quanto após alimentação. Cada estudo envolveu 32 participantes. Em ambos os estudos, nos estados de jejum e alimentado, os principais parâmetros farmacocinéticos foram calculados utilizando o Software SAS® 9.4, e a bioequivalência foi avaliada. **Resultados:** Para a avaliação de bioequivalência, um total de 31 voluntários completou o estudo em jejum, e 29 completaram o estudo na condição alimentada. Os intervalos de confiança de 90% para as razões das médias geométricas da área sob a curva do Levetiracetam (AUC_{0-T} e $AUC_{0-\infty}$) e da concentração plasmática máxima (C_{max}) estavam dentro dos limites estabelecidos de bioequivalência (80% a 125%). Foram relatados três eventos adversos durante a condução dos dois estudos, sendo um possivelmente relacionado ao medicamento em estudo e os outros dois considerados não relacionados. Todos os eventos adversos foram de intensidade leve a moderada e não impactaram significativamente a qualidade de vida dos participantes. Nenhum evento adverso grave foi relatado. **Conclusão:** Pode-se concluir que as duas formulações podem ser usadas de forma intercambiável.

Palavras-chave: anticonvulsivantes, levetiracetam, HPLC-MS, bioequivalência, farmacocinética.

Introduction

Levetiracetam is an antiepileptic drug approved by the Food and Drug Administration (FDA) as an adjunct therapy for adults with partial seizures, both in monotherapy and in combination with other antiepileptic drugs. It is used to treat partial, myoclonic, and tonic-clonic seizures, and can be administered IV or SC, with good tolerability and few drug interactions [1-6].

The extended-release formulation of levetiracetam allows for a reduction in dosing frequency by rapidly releasing a fraction of the drug (loading dose) to produce the desired pharmacological effect, while the remaining portion (maintenance dose) is released at a constant rate[1]. This sustained-release system aims to balance the rates, ensuring a continuous therapeutic response. Among the benefits of modified-release formulations are the reduction in the number of daily doses required and the decrease in plasma concentration fluctuations of the drug. These factors contribute to minimizing the occurrence of toxic and adverse effects, thereby improving patient adherence to treatment, which in turn leads to better clinical outcomes and overall disease management.

Levetiracetam binds to synaptic vesicle protein SV2A, interfering with the release of the neurotransmitter stored within the vesicle. It gains access after neurotransmitter release as the vesicles are recycled. Thus, it selectively accumulates in, and inhibits, rapidly firing neurons. [7] Levetiracetam also inhibits potassium and N-type calcium channels.[8] Anti-epileptics should not be used *prophylactically* in the absence of a history of seizures; in RCTs, they do not reduce the risk.[9] Peri-neurosurgical use is a possible exception, but results are conflicting.[10,11] If used for this indication, prophylactic levetiracetam appears more effective than phenytoin (incidence of seizures 0% vs. 16%).[12].In the present study, sponsor attempted to formulate an extended-release tablets of levetiracetam, to improve access to these medications, and this is where generic drugs stand. The objective of our work to show bioequivalence between Keppra XR and the product developed by Eurofarma.

The choice of the reference drug for this study was based on the official list of reference medications published by ANVISA**,** as established by RDC No. 35 of 2012, which was in effect during the conduct of the study. This ensured compliance with regulatory requirements and guaranteed the use of a reliable and recognized comparator for the bioequivalence evaluation.LC-MS/MS method were used to determine concentration of drug after oral dosage of Levetiracetam 750 mg Extended Release Coated Tablets of the test formulation of Eurofarma in healthy subjects and the reference formulation [Keppra XR (Levetiracetam)] from UCB Pharma SA and compare the two pharmacokinetic parameters to evaluate test and reference formulation bioequivalence under fasting condition and fed conditions for application for registration and marketing purpose.

Methods

Drugs and instruments

Test formulation of Levetiracetam 750 mg Extended Release Coated Tablets (T): Manufactured & Distributed By: Eurofarma Laboratórios S.A. Complexo Industrial de Itapevi Rodovia Presidente Castello Branco, KM 35.6 – Itaqui - Itapevi / SP. Reference formulation of Keppra XR (Levetiracetam) 750 mg Extended Release Coated Tablets(R): Generic name: Levetiracetam Trade name: Keppra XR, Manufacturer: UCB Pharma SA Braine- lAlleudBélgica Distributed by: UCB Biopharma Ltda. Avenida Presidente Juscelino Kubitschek,1327 - 5º andar- Vila Nova Conceição CEP: 04543-011- São Paulo/SP

Bioanalysis Technique: LC-MS/MS, Internal Standard: Levetiracetam D6, Detectors: AB Sciex Triple Quad 4500 and AB Sciex-4000, Anticoagulant: Na-Heparin, Solid Phase Extraction, Quantitation by: Peak area ratio, Statistical Analysis: SAS® Software 9.4.

Study Design

In both fasting and fed conditions, the study design was a single-center, open, balanced, randomized, two-period, two-treatment, two-sequence, single dose, cross-over comparative bioequivalence study of two formulations: Levetiracetam 750 mg Extended Release Coated Tablets manufactured by Eurofarma (Test Product [T]) and Keppra XR (Levetiracetam) 750 mg Extended Release coated tablets (Reference Product [R]), with a washout period of 07 days. The clinical, analytical and statistical phases of the study were conducted at Accutest Research Laboratories in India facilities.

The studies were conducted in accordance with Good Clinical Practice (as defined by the International Conference on Harmonisation)[14] and with the ethical principles of the Declaration of Helsinki[13], as well as the bioequivalence guidelines issued by the Brazilian Health Regulatory Agency (ANVISA), including RE No. 1170/2006 and its subsequent updates, and all applicable local regulatory requirements.[15] The protocol and subject informed-consent forms received appropriate approval from the Institutional Review Board/Independent Ethics Committee before the studies began. Written informed consent was obtained from all subjects prior to screening. In each study, a total of 32 healthy volunteers were enrolled, comprising 16 males and 16 females, aged between 18 and 45 years. The mean age of the subjects was 36.71 years in fasting study and 30.07 years in fed study. All participants were non-smokers, with a body mass index (BMI) ranging from 18.5 to 30.0 kg/m², with a mean BMI of 24.44 kg/m² in the fasting study and 24.40 kg/m² in the fed study.

Subjects had negative serum test results for HIV-1, HIV-2, HBsAg, hepatitis C virus, and anti-HBc IgM, as well as a negative RT-PCR test for COVID-19. They also had normal values for hemoglobin, leukocyte and platelet counts, urinalysis, serum levels of creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, fasting glucose, cholesterol, and creatinine clearance. Female subjects were excluded if pregnant or breastfeeding and were required to have a negative serum pregnancy test within 24 hours prior to dosing.

Subjects were randomized based on a randomization table generated using SAS® software version 9.4.

Exclusion criteria included history of hypersensitivity to levetiracetam, or related drugs, require medication for any ailment having enzyme-modifying activity in previous 28 days prior to dosing, any prescription or OTC medication within 14 days prior to dosing, any medical or surgical condition which interfere with the functioning of gastrointestinal tract or blood forming organs, a history of gastrointestinal, hepatic, renal, cardiovascular, pulmonary, neurological, psychiatric, metabolic, or hematological disease, history of any malignancy or other serious disease, participation in a clinical drug study within 6 months, recent (less than six months) blood donation, found positive for RT-PCR, Urine alcohol test and Urine test for drug abuse.

Enrolled subjects were admitted to the clinical facility the day before study-drug administration and were confined to the facility up to 24hrs after dosing. Each subject received either a single 750mg oral dose of levetiracetam (750mg coated tablets) test product or reference product Keppra XR (levetiracetam) on day 1 of the study. Subjects were discharged from the clinical facility after 24 hours of completion of clinical and safety evaluation in each period of the study.

Dosing regimen and restrictions

In the fasting study all medications were administered orally under fasting conditions (fasted overnight from 10.50 hours prior to dosing) and in the fed study High Fat High Calorie (HFHC) breakfast was provided to enrolled subjects 30mins prior to their schedule dosing time to eligible male and female volunteers as per the randomization schedule. A single dose was administered with 200 mL of water in sitting position in each period. Enrolled subjects were fasted for 04:00 hours post dosing. Subjects were prohibited from drinking water from 2 hours before taking medicine and within 2 hours after taking the medicine. Subjects were kept in sitting position for 4 hours post dose. After taking medicine, subjects were served breakfast, lunch, light snacks and dinner as per the study protocol requirements. The subjects remained in the clinical facility from the preceding night until 24 h after dosing; external blood sampling was performed at 36:00 and 48:00 hours in each study period. There was a washout period of seven-days between the administrations of each of the two medications. All subjects abstained from any xanthine-containing food or beverages for at least 48 hours and alcoholic products for at least 48 hours before the drug administration and throughout the sampling schedule during each period.

Blood sample collection and analysis

In each study period, blood samples were collected for pharmacokinetic assessments. For the fasting study and fed study, total of twenty-three (23) blood samples and twenty-five (25) blood samples were collected respectively. Each blood sample of 5ml blood were collected in Na-Heparin vacutainers.

In the fasting study blood samples were collected at pre dose, (collected 30 min prior to drug administration) and 01:00, 01:30, 02:00, 02:20, 02:40, 03:00, 03:20, 03:40, 04:00, 04:20, 04:40, 05:00, 05:30, 06:00, 07:00, 08:00, 10:00, 12:00, 16:00, 24:00, 36:00 and 48:00 hours after drug administration in each study period.

In the fed study blood samples were collected at pre dose, (collected 30 min prior to drug administration) and 00:30, 01:00, 01:30, 02:00, 02:30, 03:00, 03:20, 03:40, 04:00, 04:20, 04:40, 05:00, 05:30, 06:00, 06:30, 07:00, 07:30, 08:00, 10:00, 12:00, 16:00, 24:00, 36:00 and 48:00 hours post dose in each study period for pharmacokinetic assessments

The samples were centrifuged at 3500 RPM for 10 min at 5°C ± 3°C. The plasma samples were separated (two aliquots) and placed at -20 ± 5°C after each cycle of sampling and sent for analysis to Accutest Research Laboratories (I) Pvt. Ltd. A-31, M.I.D.C., T.T.C. Industrial Area, Khairane, Navi Mumbai, Maharashtra, India.

Safety monitoring

Subjects were closely monitored for adverse events and were not discharged from the study until the investigator had determined that all the adverse events had resolved or were not of clinical significance. Data on adverse events were collected through constant monitoring, volunteering of information by the study participants, and daily questioning by the medical staff. Additionally, the adverse events could be identified by investigator review of vital signs, electrocardiogram (ECG), laboratory, and other data.

Method validation

Levetiracetam concentration was measured in plasma samples by using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS), AB Sciex Triple Quad 4500 and AB Sciex-4000. The internal standards (IS) used was Levetiracetam-D6. The extraction of the samples was done by solid-solid techniques. The assay was validated over a concentration range of 500 to 59916 ng/mL. The analyst was kept blind during the sample analysis.

Pharmacokinetic Analysis

The pharmacokinetic analyses for both fasting and fed studies were performed by using SAS® 9.4 version program. The primary pharmacokinetic parameters compared between treatments were maximum plasma concentration (C_{max}), the area under the concentration-time curve (AUC) from time zero to the last quantifiable time point after dosing (AUC_{0-t}). Other pharmacokinetic parameters examined were time to reach C_{max} (T_{max}), apparent terminal half-life ($t_{1/2}$), and elimination rate constant (kel). All pharmacokinetic parameters were determined by non-compartmental methods. Values below the quantification limit (<501.426 ng/mL) were set to zero for calculation purposes.

Statistical Analysis

Calculation of pharmacokinetic parameters and statistical analysis for establishing bioequivalence were performed using the statistical package SAS® version 9.4. The PROC GLM procedure was used for analysis of variance (ANOVA) and estimation of least square mean differences (Test–Reference) between the test and reference formulations for the log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of levetiracetam, and for the untransformed parameter T_{max}. The corresponding standard errors of the differences were also computed.

Descriptive analyses, including mean, median, standard deviation (SD), coefficient of variation (CV), minimum, and maximum, were performed for all pharmacokinetic parameters. The primary pharmacokinetic parameters were C_{max} and AUC0-t. Secondary outcomes included $AUC_{0–inf}$, $AUC_{0–t}$/$AUC_{0–inf}$, $AUC_{0–inf}$/$AUC_{0–t}$, T_{max}, Kel, and T½.Statistical significance was evaluated based on the 90% confidence intervals (CIs) for the geometric mean ratio (GMR) of the log-transformed pharmacokinetic parameters C_{max} and AUC0–t between the test and reference products. Bioequivalence was concluded if the 90% CIs were entirely contained within the predefined acceptance range of 80.00% to 125.00%.

Results

The calibration curve was linear over the range of 500 to 59,916 ng/mL (r≥0.9994). Intra- and inter-assay precision and accuracy were within acceptable limits, with coefficients of variation (CV) and relative errors (RE) below 15% across all quality control levels, in accordance with regulatory guidelines.

All subjects were screened and evaluated for eligibility within 21 days prior to study drug administration. Enrolled subjects who met all eligibility criteria at screening were randomly assigned in a 1:1 ratio to receive either Test Product Levetiracetam or reference product (Keppra XR). Randomization was carried out according to a computer-generated randomization scheme (SAS® 9.4 Software).

Thirty-two (32) volunteers (16 males and 16 females), aged between 18 and 45 years, were enrolled in each study. All subjects underwent a clinical examination to assess their general health condition. Additionally, vital signs, ECG, and laboratory tests were performed to confirm eligibility. A total of 31 subjects completed the fasting study, and 29 subjects completed the fed study; both groups were considered for bioequivalence evaluation.

In fasting study, one subject was dropped out of the study due to Adverse Event. Hence, thirty-one (31) subjects were considered for final statistical analysis of fasting study. In the fed study, one subject was withdrawn due to protocol non-compliance on the day of check-in in Period-I. Two dropouts occurred during the study (one for personal reasons and the other due to an adverse event). Hence, a total of twenty-nine (29) subjects were considered for the final statistical analysis in the fed study.

Table 2 represents summary statistics for pharmacokinetic parameters of single-dose Levetiracetam. Levetiracetam was absorbed after oral administration, with adequate concentration levels achieved between 02:00 and 12:00 hours for the Test Product and between 02:40 and 10:00 hours for the Reference Product in the fasting study, and between 04:20 and 12:00 hours for the Test Product and between 04:20 and 10:00 hours for the Reference Product in the fed study.

A total of 32 healthy adult participants were enrolled in both studies, 31 subjects were considered for statistical analysis for fasting study and 29 subjects were considered for statistical analysis for fed study. The Table 2 and Table 3 shows the geometric mean ratios between the test and the reference formulations (T/R) of C_{max}, AUC_{0-t} and AUC_{0-inf} for log-transformed data, as well as the intra subject coefficient of variations (CV). The 90% CI ratios of geometric mean C_{max}, AUC_{0-t} and AUC_{0-inf} were within the range of 80-125%, which met the regulatory criteria for bioequivalence.

No significant formulation or period-sequence effects were detected at 5% level of significance based on ANOVA of C_{max}, AUC_{0-t} and $AUC_{0-inf.}$

The 90% Confidence Interval of the geometric mean ratios of the two parameters (C_{max} and AUC_{0-t}) fell within the predetermined range of 80.00 to 125.00%. All probability values were 0.99 (power > 99%), suggesting that the sample size was sufficient for the purpose of the study.

No significant differences were observed at the 5% level of significance for the factor "period" for log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. No significant differences were observed at the 10% level of significance for the factor "sequence" for log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. No significant differences were observed at the 5% level of significance for the factor "treatment" for log transformed pharmacokinetic parameters AUC_{0-t} and AUC_{0-inf}. However significant differences were observed at the 5% level of significance for the factor "treatment" for log transformed pharmacokinetic parameters C_{max}.

A significant treatment effect can be present when the treatment mean square is small. In other words, the ANOVA procedure carried out is nothing but the evaluation identical to the power approach, so it can be said that the significant difference can occur at the moment the variability is low or the ratio of test to reference is low.

Table 1. Results for pharmacokinetic measures obtained after oral administration of both reference and test formulations of Levetiracetam 750 mg Extended Release Coated Tablets (Schedule time) for fasting and fed study.

Pharmacokinetic Parameters	Mean ± SD (CV%) (N=31) (Schedule blood sample collection time)		Mean ± SD (CV%) (N=29) (Schedule blood sample collection time)	
	Fasting		Fed	
	Keppra XR (Reference-R)	Levetiracetam Formulation (Test-T)	Keppra XR (Reference-R)	Levetiracetam Formulation (Test-T)
C_{max} (ng/mL)	13850.333 ± 2763.622 (19.953)	14210.519 ± 2600.805 (18.302)	15548.136 ± 2714.583 (17.459)	14791.459 ± 2927.299 (19.790)
AUC_{0-t} (h·ng·mL^{-1})	271564.573 ± 66716.166 (24.567)	275896.268 ± 62826.872 (22.772)	282599.251± 50834.419 (17.988)	279772.933 ± 50869.924 (18.183)
AUC_{0-inf} (h·ng·mL^{-1})	284742.973 ± 69622.711 (24.451)	287122.777 ± 65943.666 (22.967)	292608.787± 51503.841 (17.602)	291710.085 ± 49732.062 (17.048)
T_{max} (h)	4.801 ± 1.840 (38.331) (4.330)[a] (2.670 – 10.000)[b]	5.151 ± 2.258 (43.834) (4.670)[a] (2.000 – 12.000)[b]	6.259 ± 1.343 (21.454) (6.500)[a] (4.330 – 10.000)[b]	6.839 ± 1.721 (25.165) (6.500)[a] (4.330 – 12.000)
Kel (hrs^{-1})	0.083 ± 0.011 (13.275)	0.088 ± 0.012 (14.091)	0.091 ± 0.013 (14.666)	0.091 ± 0.014 (15.387)
$T_{1/2}$ (h)	8.473 ± 1.191 (14.051)	8.069 ± 1.195 (14.815)	7.741 ± 1.155 (14.925)	7.804 ± 1.160 (14.868)

[a]Median; [b]Range of Tmáx.

Figure 1. Mean plasma concentration of Levetiracetam after oral administration test and reference formulation in 31 healthy volunteers under fasting conditions.

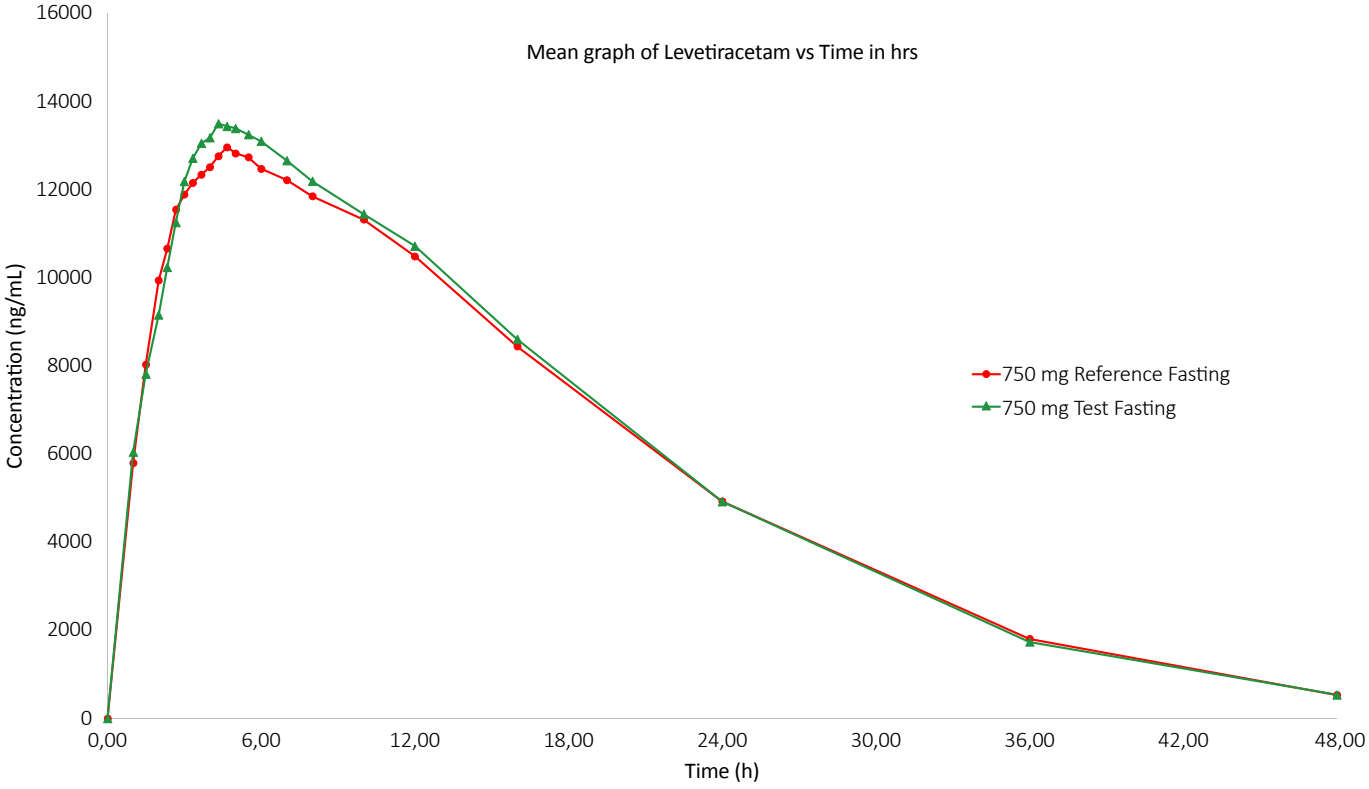

Figure 2. Mean plasma concentration of Levetiracetamw after oral administration test and reference formulation in 29 healthy volunteers under fed conditions.

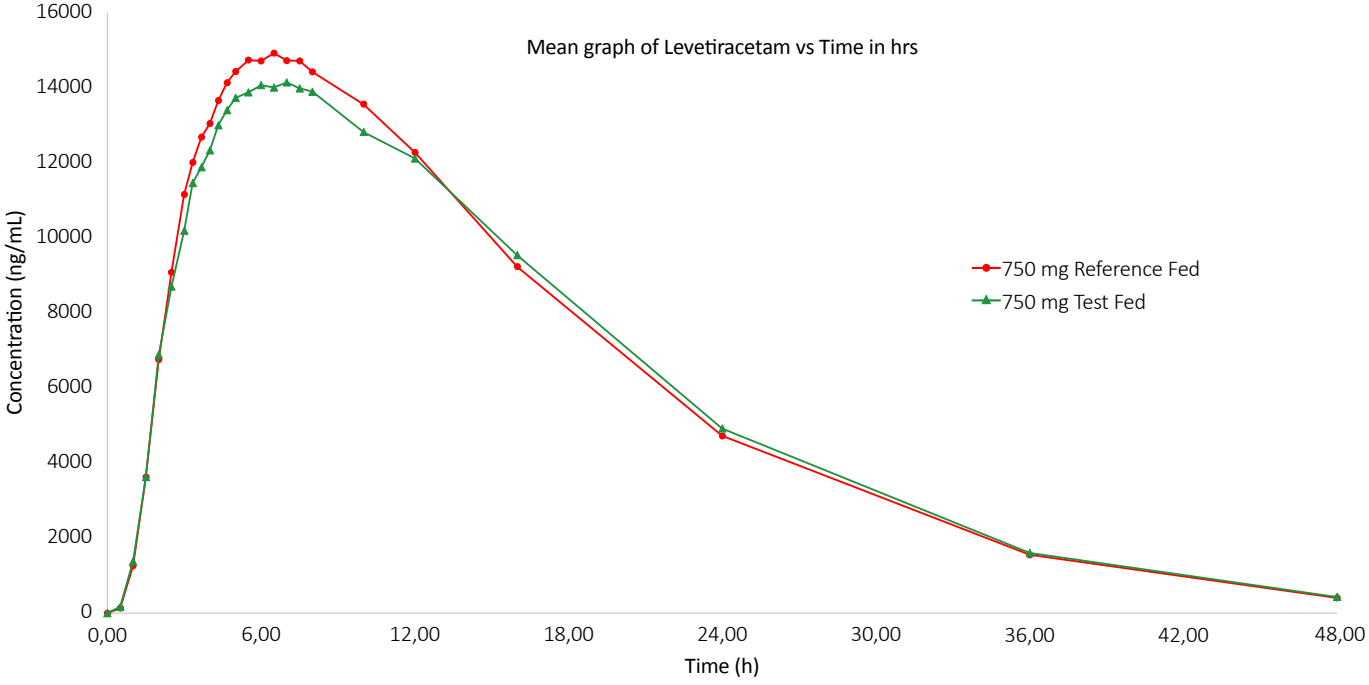

Table 2. Bioequivalence results of reference and test formulations of Levetiracetam 750 mg Extended Release Coated Tablets under fasting conditions (N=31).

Parameters	Geometric LSM		T/R Ratio (%)	CI (90%)	CV (%) Intra	Power (%)	p-Value	Bioequivalence
	Levetiracetam Formulation (Test-T)	Keppra XR (Reference-R)						
C_{max} (ng/mL)	13965.8916	13584.2266	102.8096	99.0300 – 106.7335	8.69	100.00	0.2188	Yes
AUC_{0-t} (ng*hr/mL)	268924.792	263173.354	102.1854	98.8805 – 105.6008	7.62	100.00	0.2730	Yes
AUC_{0-inf} (ng*hr/mL)	279862.097	276088.234	101.3669	98.1955 – 104.6407	7.37	100.00	0.4738	Yes

Table 3. Bioequivalence results of reference and test formulations of Levetiracetam 750 mg Extended Release Coated Tabletsunder fed conditions (N=29).

Parameters	Geometric LSM		T/R Ratio (%)	CI (90%)	CV (%) Intra	Power (%)	p-Value	Bioequivalence
	Levetiracetam Formulation (Test-T)	Keppra XR (Reference-R)						
C_{max} (ng/mL)	14493.3459	15288.5015	94.7990	92.9722 – 96.6616	4.3495	100.00	<.0001	Yes
AUC_{0-t} (ng*hr/mL)	275158.544	278055.946	98.9580	96.6736 – 101.2963	5.2217	100.00	0.4515	Yes
AUC_{0-inf} (ng*hr/mL)	287486.629	288113.162	99.7825	97.6580 – 101.9533	4.8113	100.00	0.8645	Yes

However, as the decision of equivalence was based on the 90% confidence interval by Schuirmann two-sided t test and the 90 % CI is within the acceptance criteria i.e., 80% to 125% these significant effects can be ignored.

The 90% Confidence Interval of the geometric mean ratios of the two parameters (C_{max} and AUC_{0-t}) fell within the predetermined range of 80.00 to 125.00%. All probability values were 0.99 (power > 99%), suggesting that the sample size was sufficient for the purpose of the study.

Three non-serious adverse events (AEs) were reported: two in the fasting study and one in the fed study. In the fasting study, mild elevated random plasma glucose (233 mg/dL) and a positive RT-PCR COVID-19 test were observed; both events were considered unlikely related to study drug and resolved without intervention. In the fed study, one moderate AE of vomiting after dosing was possibly related to the study medication and resolved completely. No serious or clinically significant AEs occurred. Both the test (Levetiracetam 750 mg ER) and reference (Keppra XR 750 mg ER) products were well tolerated with no relevant differences in safety profiles.

Discussion

Evaluations of the bioequivalence of a test drug and a reference drug are required to exclude any clinically important differences in the rate or extent to which the active entity of the drugs becomes available at the action. Regulatory agencies consider two formulations of the same drug are considered to be bioequivalent or therapeutically equivalent if they exhibit a comparable extent and rate of absorption, when they are administered in the same molar dose and under similar experimental conditions that they are unlikely to produce clinically relevant differences in regard to tolerability and efficacy.

For this ANVISA regulatory authorization, reference is made to the clinical studies and experience with the innovator product Keppra XR (levetiracetam). Keppra XR is a well-known medicinal product with an established favorable efficacy and safety profile. The bioequivalence for the 750 mg strength has been shown to be in compliance with the requirements of the ANVISA guidelines. Eurofarma Laboratories SA - Brazil demonstrated through a bioequivalence study that the pharmacokinetic profile of the test product (levetiracetam 750 mg extended-release coated tablet) is similar to the pharmacokinetic profile of this reference product [Keppra XR (levetiracetam)].

The reference product, Keppra, was granted marketing authorization by the Brazilian Health Regulatory Agency (ANVISA), according to the official List A of Reference Medicines and the applicable regulatory framework[16]. Also, the study protocol for conducting bioequivalence study with test product levetiracetam of Eurofarma and the reference product Keppra was approved by DCGI on the basis of safety data submitted.

These two studies showed that the test preparation of Levetiracetam and the reference preparation are bioequivalent when administered under fasting and fed condition; both Levetiracetam formulations display a pharmacokinetic behavior after single dosing. The pharmacokinetic parameters obtained with the test and reference formulations were not significantly different, which reflects the comparable pharmacokinetic characteristics of the two formulations.

The single dose of the test and reference product of levetiracetam 750 mg extended release coated tablet was well tolerated. There was not relevant difference between the test and the reference product in the safety parameter.

In accordance with the regulatory guidelines in force at the time of the study, bioequivalence studies were generally conducted in healthy volunteers under single-dose conditions. This approach aimed to minimize variability and focused on assessing the rate and extent of drug absorption rather than clinical efficacy.

Multiple-dose studies or trials involving patients were only required in specific scenarios, such as drugs with complex pharmacokinetics or narrow therapeutic indices. Therefore, although the present study did not evaluate multiple doses or include patients, its design aligns with ANVISA's recommendations for bioequivalence assessments of generic drugs in force at the time of the study, as outlined in RE No. 1,170/2006.

The 90% CI ratios of geometric mean C_{max}, AUC_{0-t} and AUC_{0-inf} were within the range of 80-125%, which met the regulatory criteria for bioequivalence.

The development and introduction of generic drugs following patent expirations represent a significant advancement for public health by increasing treatment options, promoting competition, and expanding access to essential therapies. This leads to substantial cost reductions, making medications more affordable for a broader segment of the population and contributing to the sustainability of healthcare systems, both in hospital and outpatient settings.

The Generic Drugs Law (Law No. 9,787/1999) regulates that generic medicines must be marketed at a price at least 35% lower than that of the reference drugs, thereby ensuring an immediate reduction in costs for healthcare systems and patients. Furthermore, competition among generic manufacturers drives continuous improvements in product quality and innovation, enhancing the economic and clinical benefits for the population.

In this context, the demonstration of bioequivalence between the two levetiracetam formulations supports the availability of more affordable options for the Brazilian population.

Given the lower production and investment costs associated with generic products such as those from Eurofarma, the introduction of this generic levetiracetam may generate significant cost-effectiveness and budgetary benefits, expanding access in both hospital environments and primary and outpatient care.

Conclusion

The statistical analysis of the results which carried out on C_{max} and AUC_{0-t} using the ANOVA method demonstrated that the test product levetiracetam 750 mg extended release coated tablets manufactured by Eurofarma Laboratories SA and the reference product Keppra XR (levetiracetam) 750 mg extended release coated tablets are bioequivalent, since they release equivalent quantities of active ingredient to the system circulation at equivalent rates, which was proved by calculating the 90% Confidence Interval of the geometric mean ratios for C_{max} and AUC_{0-t} which falls within the range of 80.00%- 125.00%.

This study has demonstrated the bioequivalence of the Levetiracetam 750 mg Extended Release Coated Tablets formulation manufactured by Eurofarma Laboratories SA, Brazil, and the reference product Keppra XR (Levetiracetam) manufactured by UCB Pharma SA. It thus can be concluded that the two formulations can be used interchangeably. In these studies, no clinically significant changes in vital signs, physical examinations, ECGs or important medical events were reported, hence it is also established that both the products are safe after administration in healthy volunteers under fasting and fed conditions.

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Contributors

C.K.A. and L.C.V. contributed to the conception and conduct of the study, as well as to data interpretation.

N.C.A. and F.R. were responsible for text revision and editing.

P.A. and N.K.T. were responsible for drafting the manuscript.

All authors critically reviewed the manuscript, approved the final version to be published, and take responsibility for the accuracy and integrity of the information presented.

Conflict of interest statement

Camila K. Aihara, Fabiana Roveda, Ligia C. Val, and Natália C. Aoki declare employment with Eurofarma Laboratórios S.A., the study sponsor.

Pratikkumar Asari and Naba Kumar Talukdar declare employment with Accutest Research Laboratories Private Limited, the organization contracted to conduct the study.

The authors declare that there are no other conflicts of interest related to this article.

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