Bioequivalence of Lamotrigine 50-mg Tablets in Healthy Male Volunteers: a Randomized, Single-Dose, 2-Period, 2-Sequence Crossover Study

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Key words
- lamotrigine
- safety
- pharmacokinetics
- bioequivalence
- epilepsy
- bioavailability

Abstract

Objective: To compare the bioavailability of two 50-mg lamotrigine dispersible tablet formulations (Epilepax®, Ivax-TEVA Argentina Laboratories, Argentina, as a test formulation, and Lamictal®, GlaxoSmithKline, UK, as a reference formulation) in 24 healthy male volunteers.

Material and Methods: This study was a randomized, 2-period, 2-sequence crossover design that was open for subjects and investigators, but blind for the bioanalytical lab. Serum samples were obtained over a 120-h interval. A 9-day wash-out period was allowed between treatments. The concentrations of lamotrigine were analyzed by high-performance liquid chromatography followed by ultraviolet-visible detection. Lamotrigine time-concentrations curves were obtained and the following pharmacokinetic parameters were calculated: AUC_{0-t}, AUC_{0-inf} and Cmax. Bioequivalence was declared if the 90% confidence interval (CI) of the mean test/reference ratios for AUC_{0-t}, AUC_{0-inf} and Cmax were within 80.00–125.00%.

Results: The geometric mean and respective 90% CI of test/reference percent ratios were 100.83% (92.53–107.88%) for AUC_{0-t}, 99.91% (93.79–108.40%) for AUC_{0-inf}, and 95.62% (90.91–100.57%) for Cmax. No serious adverse events were observed. 1 patient reported a mild rash following the administration of each formulation.

Conclusion: This single dose study found that the test and reference products met the regulatory criteria for bioequivalence in this sample of fasting healthy volunteers. These results suggest that bioequivalence studies evaluating 50-mg doses of Lamotrigine are feasible and recommended, since such doses may minimize the risk of severe rash or Stevens-Johnson Syndrome. This study was registered at the Argentinean Clinical Trials National Registry (www.anmat.gov.ar), No 1666/2008.

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Introduction

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine), a phenyltriazine derivative, inhibits voltage-activated sodium channels and, possibly, calcium channels [1]. By doing so, it prevents the release of excitatory amino acids, particularly glutamate [2]. Lamotrigine has a broad spectrum of activity, which makes it useful for a variety of seizure types, including partial crisis, secondary generalized epilepsy, tonic-clonic, absence or myoclonic crisis and Lennox-Gastaut syndrome [3]. Usual doses for this indication are 100–500 mg/day [4]. Lamotrigine is also indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in doses of 200–400 mg/day [5].

Lamotrigine is rapidly and completely absorbed from the gastrointestinal tract after oral administration, with Tmax values of 2.2 h (range 0.25–12.0 h) [6]. The bioavailability of lamotrigine is not affected by food [6] and the pharmacokinetics are dose proportional. After absorption, the Vd of lamotrigine is 1.0–1.3 L/kg, and its extent of plasma protein binding is 55% [7]. Lamotrigine concentrations in the cerebrospinal fluid (CSF) are similar to free non-protein-bound concentrations and the CSF:plasma concentration ratio is 0.43 [8]. Lamotrigine undergoes extensive hepatic metabolism via glucuronidation, with N-2 glucuronide as the primary metabolite [9]. All metabolites are inactive. In healthy volunteers, the elimination half-time is 32.8 h (range 14.0–103.0 h) [6]. Autoinduction or coadministration of other antiepileptic drugs (AEDs) such

as phenytoin and carbamazepine may reduce lamotrigine plasma concentrations [1]; the coadministration of lamotrigine with enzyme inhibitors such as valproate may increase lamotrigine plasma levels.

Lamotrigine is generally well tolerated in both pediatric and adult patients with epilepsy [6] or Bipolar Disorder [10]. Lamotrigine does not cause weight gain, has not been associated with reproductive endocrine abnormalities [11,12], and appears to enhance mood in some patients with epilepsy [13,14]. Nonetheless, like other AEDs, including carbamazepine and phenytoin, lamotrigine has been associated with serious rash, which, although very rare, is the most common adverse event leading to discontinuation of therapy [15,16]. Most rashes are benign and self-limited [16,17], but cases of potentially lethal Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. In addition to affecting quality of life and compliance in treated patients, such safety concerns may limit drug administration to healthy subjects for research purposes.

The objective of this study was to establish lamotrigine bioequivalence after single 50-mg oral doses of 2 different dispersible tablets formulations: Epilepax, manufactured by Ivax-TEVA Laboratories, Argentina [test formulation] and Lamictal, manufactured by GlaxoSmithKline, United Kingdom [reference formulation].

Methods

Study subjects

24 healthy male volunteers were enrolled in this study. All subjects were in good physical condition, as determined by complete physical and clinical examinations, including medical history, blood pressure and ECG, chest X-ray, urinalysis, and blood biochemical, virological and hematological examinations before the study. Subjects were instructed to abstain from all drugs for at least 2 weeks prior to and during the study. Subjects with a history of drug or alcohol abuse or drug hypersensitivity were excluded from the study. Informed consent was obtained from each subject before enrollment. The study protocol was approved by an independent Ethics Committee and the national drug regulatory authority (ANMAT). This study was registered at the Argentinean Clinical Trials National Registry (www.anmat.gov.ar), No 1666/2008.

Drugs

All subjects received one 50-mg lamotrigine tablet of the test or reference formulation and then another 50-mg tablet of the reference or test formulation in a subsequent period. The test formulation was Epilepax (dispersible tablets, Lot R331200), manufactured by Ivax-TEVA, Argentina, and the reference formulation was Lamictal (dispersible tablets, Lot 0006), manufactured by GlaxoSmithKline, United Kingdom. The reference preparation was purchased from a local commercial supplier.

Study design

This was a randomized, balanced, oral single-dose, 2-period crossover study in 24 healthy volunteers under fasting conditions. The study was open for subjects and investigators, but blinded for the bioanalytical laboratory. After an overnight fast, lamotrigine 50 mg was orally administered according to a randomized crossover design with at least a 9-day washout period between phases. No food was allowed until a standardized meal was given 5 h after drug administration. Vital signs were checked before and every 12 h during the first 24 h of the study period. Volunteers remained hospitalized for 24 h. Blood samples (7 ml) from a suitable antecubital vein were collected into polypropylene tubes before and 1, 2, 2.5, 3, 4, 5, 8, 24, 48, 96 and 120 h after dosing. Serum samples were collected and stored at −20 °C until testing.

Safety was assessed by performing full physical examination as well as blood biochemical (plasmatic albumin level glycemia, seric BUN, plasmatic creatinine level, plasmatic bilirubin level, plasmatic hepatic enzyme levels, protrombin time, KPTT, plasmatic total protein level and serum cholesterol level), virological (Hepatitis B and C virus, HIV) and hematological (red blood count, white blood count, red cell sedimentation) tests at baseline and after the second period.

Analytical method

The extraction method was developed for sample preparation before analysis. Briefly, a 400-µL volume sample of serum from the subjects or of various concentrations of working standard of lamotrigine in plasma was transferred to a 10-mL tube, followed by the addition of 20 µL of 500 µg/mL chloramphenicol (internal standard) solution and 2.5 mL of diethyl-ether/dichloromethane (70/30; v/v). After mixing for 40 s using a vortex mixer, the solution was centrifuged for 1 min at 2 000 g. The supernatant was transferred into a 15-mL test tube and dried by 45 ° air flow. The reconstitution was completed by adding 400 µL of mobile phase. The resulting solution was injected into a high-performance liquid chromatography (HPLC) system for analysis.

An HPLC method was developed and validated for the determination of the extracted serum samples. Validation of the method followed Food and Drug Administration guidelines for bioanalytical method validation.[18] The HPLC system consisted of a quaternary pump, an ultraviolet-visible (UV) detector equipped with column thermostat and an automatic sample injector fitted with a 100-µL sample loop. The chromatographic separations were conducted on an ACE 5 CN column (100 mm × 4.6 mm id). The mobile phase was tri-distilled water, 0.5 M phosphate buffer and acetonitrile. Injection volume was 110 µL. All separations were performed at the following flow rates: minutes 0–2: 1.2 mL/min; minutes 2–3: 2.5 mL/min; minutes 3–4: 2.2 mL/min; and minute 4: 1.2 mL/min. Column conditions were maintained at room temperature (25 ± 2 °C). The UV detector was operated at wavelength of 306 nm.

Spiked serum samples at concentrations of 0.1, 0.5, 1.0, 5.0, 10.0 and 50.0, µg/mL, were used for constructing calibration curves. The ratios of the peak area of lamotrigine to the peak area of the internal standard were plotted against lamotrigine concentrations, and linearity was assessed by a least squares regression analysis over the concentration range 0.5–50.0 µg/mL. Accuracy was determined by calculating the difference between the amount added to blank serum and the amount found. The extraction recovery was determined by comparing the peak areas of extracted serum standards to the peak areas of post-extraction serum blanks spiked at corresponding concentrations. Within-day and between-day precisions were calculated as the % coefficient of variation (%CV) of replicate measurements.

Pharmacokinetic analysis

Lamotrigine pharmacokinetic parameters were calculated from individual serum concentrations using a non-compartmental

model and analyzed with WinNonlin 6.2 (Pharsight Corporation, Mountain View, CA, USA). The areas under the serum concentration-time curve were calculated from time 0 to the last quantifiable time point (AUC_{0-t}) using the trapezoidal rule. From the terminal log-decay phase, a first-order clearance rate constant (Ke) was estimated by linear regression and the terminal half-life (T1/2) was estimated using the equation $T1/2 = \ln 2 \times Ke^{-1}$. The AUC from zero time to infinity (AUC_{0-inf}) included an extrapolated area from the last serum drug concentration to infinity using the Ke estimated from the slope (β) of the terminal log-linear phase of the semilog plot of concentration vs. time. The maximum serum concentrations (Cmax) and time to maximum serum concentrations (Tmax) were observed from the measured serum concentrations following lamotrigine administration.

Statistical analysis

We calculated that 24 volunteers would be needed for this study, assuming a T/R ratio of 95%, an intrasubject variability coefficient of ≤22.5%, an alpha of 5%, and a desired power of 80%. 26 subjects were enrolled in order to compensate for possible drop-outs.

A linear analysis of variance (ANOVA) was used to analyze the logarithmically-transformed AUC_{0-t}, AUC_{0-inf} and Cmax of lamotrigine data, accounting for sources of variation due to formulation, subjects and study period. Values for Tmax were compared using the Wilcoxon signed rank sum test. Residual variances from ANOVAs were used to calculate confidence intervals for the difference in formulation means on the log scale; 90% confidence intervals (90% CI) were constructed for AUC_{0-t}, AUC_{0-inf} and Cmax. Bioequivalence was declared if 90%CI of mean test/

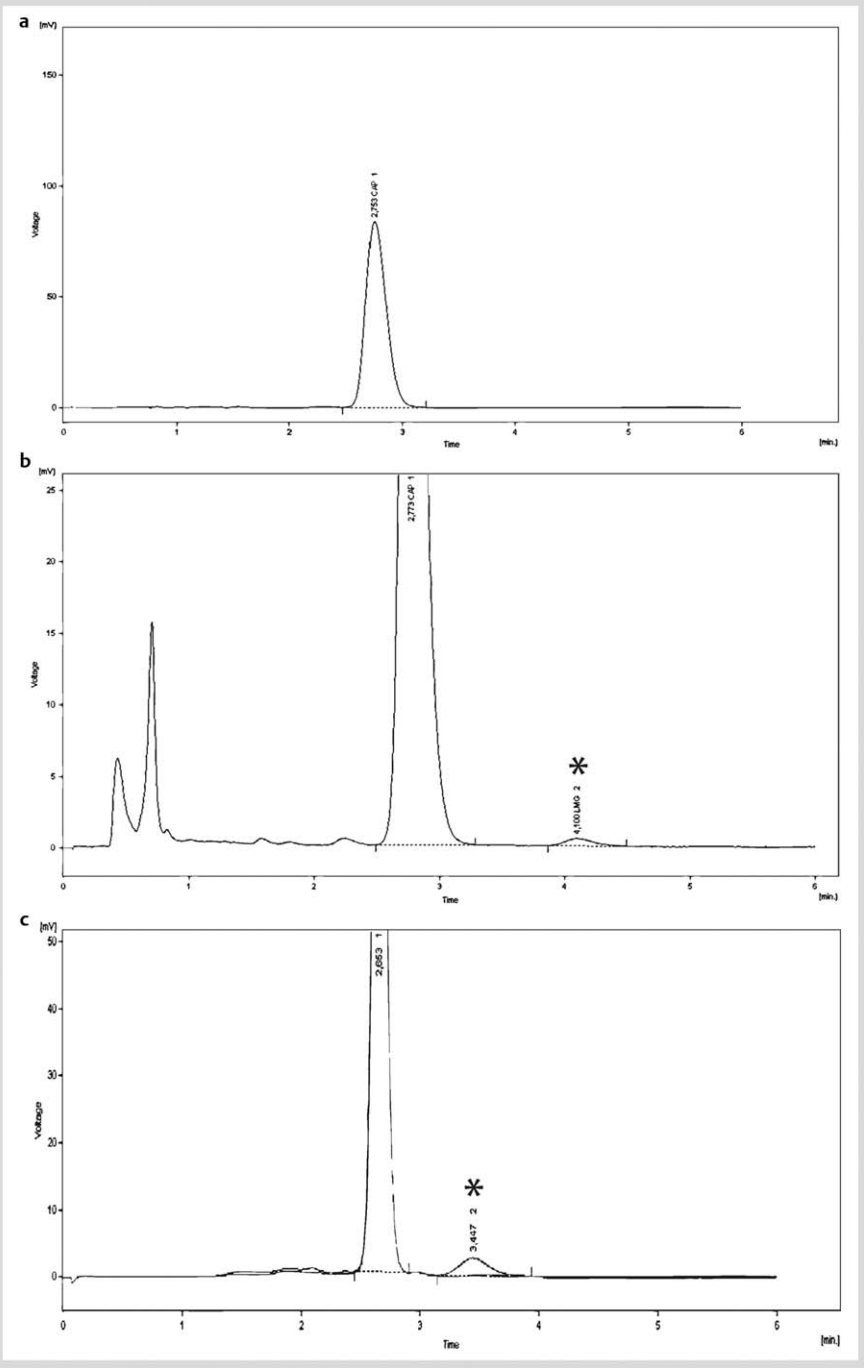

Fig. 1 Chromatograms corresponding to blank sample with internal standard **a**, control sample at the low limit of quantification **b**, and a subject's sample **c**. Peaks corresponding to lamotrigine are marked with an asterisk (*).

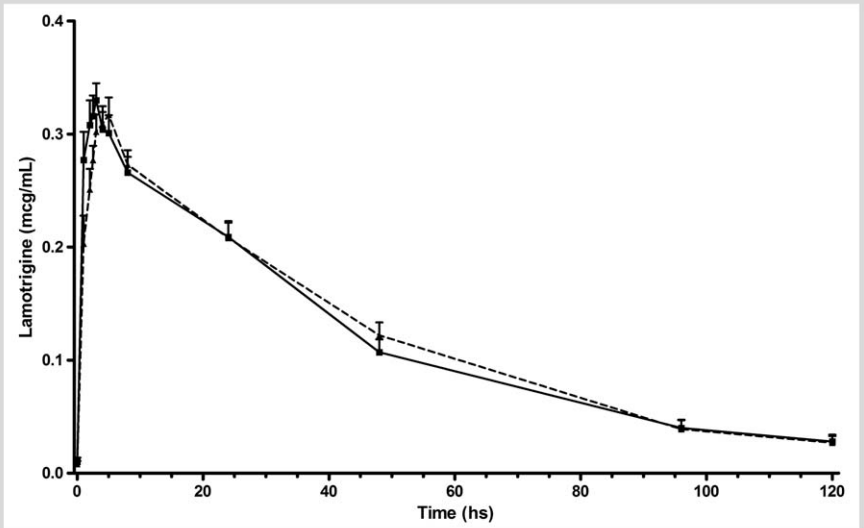

Fig. 2 Time-concentration curves of lamotrigine after administration of reference (■) and test (▲) 50-mg dispersible tablet formulations. Means and standard errors of the mean are shown for each time point.

reference ratios for AUC_{0-t}, AUC_{0-inf} and Cmax were within 0.800–1.2500. Schuirmann's test was used to formally test bioequivalence.

Bioequivalence was evaluated by means of WinNonlin 6.2. Other statistical tests were performed by SPSS 14.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Originally, 26 subjects were included and randomized into the study, but 2 of the 26 did not complete the study due to medication-unrelated non-serious adverse events (AEs). One subject was withdrawn after the first period because of a moderate hypertensive crisis that was judged to be not related to study medications. He had received test formulation. The other subject was withdrawn during the washout period because he had to be treated by amoxicillin due to a streptococcal sore throat, unrelated to study medication. He had received reference formulation.

No major protocol deviations were observed. The final sample consisted of 24 subjects of mean age 39.2 years old (median = 39.5 yrs, standard deviation = 8.8 yrs, interquartile range = 10 yrs), with mean body weight = 75.8 kg (median = 77 kg, standard deviation = 9 kg, interquartile range = 13.5 kg) and mean body mass index = 25.6 (median = 25.9, standard deviation = 2.9, interquartile range = 4.9).

Analytical method validation results

The assay was validated over the concentration range 0.5–50.0 µg/mL. The calibration curve was linear and had a correlation coefficient (r^2) of 0.9997. The accuracies were 96%, 101% and 99% for lamotrigine 0.5, 5.0 and 50.0 µg/mL quality control (QC) solutions, respectively. Within-day precisions were 8.9%, 2.6% and 1.5%, respectively, and between-day precisions were 4.4%, 0.7% and 0.7%, respectively, for the 3 QC solutions. The absolute recoveries (%CV) were 99.3% (11.8%), 99.5% (1.3%), and 100.4% (1.2%), respectively, for the 3 QC solutions. Typical chromatograms of blank serum with the internal standard, control at the lower limit of quantification, and a subject's sample are shown in **Fig. 1**.

Pharmacokinetic results

Mean serum concentration-time curves for both lamotrigine formulations are shown in **Fig. 2**. Geometric means and 95% confidence intervals values for pharmacokinetic parameters of each formulation are shown in **Table 1**.

Individual values of AUC_{0-t}, AUC_{0-inf}, Cmax or Tmax for each subject after administration of test or reference formulations are shown in **Fig. 3**. ANOVAs of natural logarithm-transformed pharmacokinetic parameters did not show any period, sequence or formulation effect. **Table 2** summarizes the bioequivalence analysis of AUC_{0-t}, AUC_{0-inf} and Cmax for lamotrigine. 2 one-sided tests (Schuirmann tests) proved bioequivalence among formulations for AUC_{0-t}, AUC_{0-inf} and Cmax.

Safety results

No serious AEs were observed. On the other hand, 9 non-serious AEs were observed in 7 patients (3 cases of headache, 3 cases of hypertension, 2 cases of cutaneous rash and 1 case of knee twisting). Only rash cases were considered possibly related to the study medication and occurred in the same subject, following administration of each formulation. This subject was not excluded from the study after the rash, as it was very mild and self-limited. There were no clinically significant abnormalities or changes in vital signs, physical examination or laboratory tests among any of the subjects.

Discussion

This study aimed to study the bioequivalence of two 50-mg dispersible tablets formulations of lamotrigine in 24 healthy volunteers. Nearly overlapping time-concentration curves (**Fig. 1**) and 90% CIs of test/reference ratios for the pharmacokinetic parameters not exceeding the pre-defined limits (**Table 2**) were observed. Therefore, according to international guidelines for claiming bioequivalence [19,20], the bioavailability of these lamotrigine formulations appears to be comparable, both in terms of rate and extent. A difference of about 2-hs was observed in Tmax. The clinical significance of such difference is unknown as Tmax for lamotrigine is highly variable [6].

	Lamictal (reference formulation)	Epilepax (test formulation)	z-value (p-value)
AUC_{0-t} (mcg/mL*h^{-1})			–
Geometric mean	12.91	13.21	
95 % CI	10.49–15.87	10.56–16.53	
AUC_{0-inf} (mcg/mL*h^{-1})			–
Geometric mean	14.14	14.33	
95 % CI	11.13–17.96	11.17–18.38	
Cmax (mcg/mL)			–
Geometric mean	0.37	0.35	
95 % CI	0.33–0.40	0.32–0.38	
Tmax (h)			
Median	2.00	4.00	2.50
P25 – P75	1.75–3.00	2.38–5.00	(0.01)
Ke (h^{-1})			
Median	0.025	0.027	0.48
P25 – P75	0.015–0.081	0.018–0.078	(0.63)
T1/2 (h)			
Median	28.01	26.12	1.06
P25 – P75	8.56–44.76	8.88–38.34	(0.29)

T1/2 = serum half life. 95 % CI = 95 % Confidence Interval. P25 – P75: Percentiles 25 and 75. Statistical comparisons were performed by means of the Wilcoxon Signed Ranks test

Table 1 Pharmacokinetic parameters of the studied formulations for 24 subjects after oral ingestion of lamotrigine 50-mg tablets.

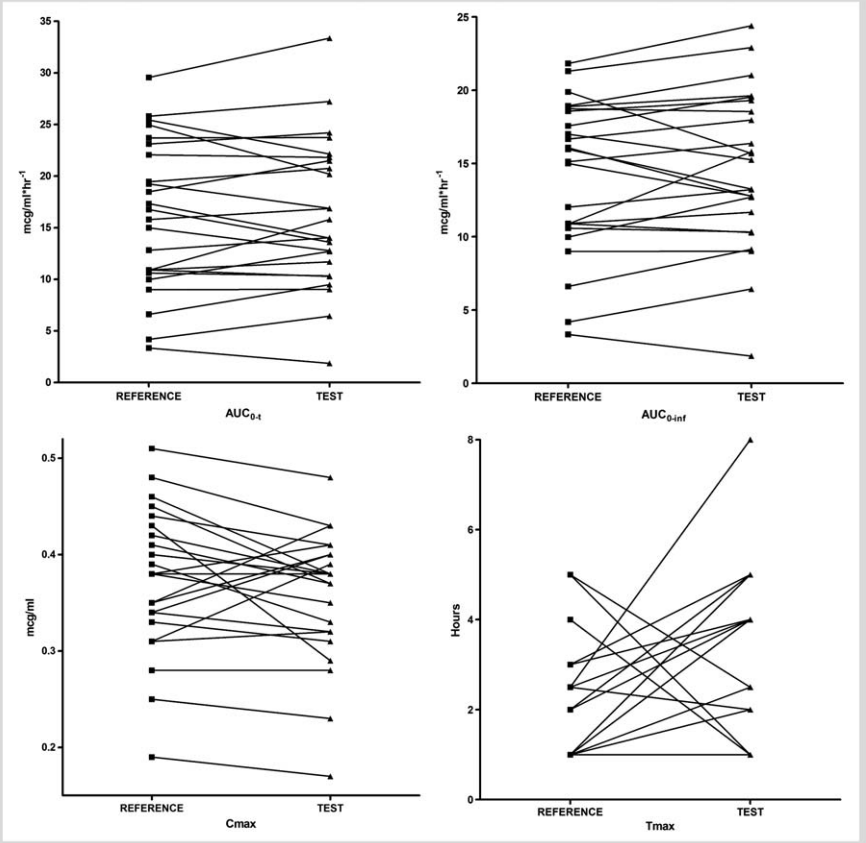

Fig. 3 Individual values of AUC_{0-t}, AUC_{0-inf}, Cmax or Tmax for each subject after administration of test and reference formulations.

In this study, low doses of lamotrigine were used due to safety concerns. In early epilepsy clinical trials, non-serious rash was reported in 10 % of patients and rash leading to hospitalization or Stevens-Johnson syndrome was reported in 0.3 % of adult patients and 0.8 % of pediatric patients taking lamotrigine [21] and in 0.1 % of bipolar disorder patients [10]. Serious cases of rash were almost always observed within the first few weeks of initiation of lamotrigine and appeared to be associated with the use of high initial doses, rapid dose-escalation and concomitant administration of valproate [16].

In recent years, several studies have been conducted in healthy volunteers for research purposes using 25–100 mg lamotrigine doses for up to 7 days [7, 22–31]. Among the 180 exposed subjects, only 1 case of non-serious rash was reported. Therefore, including this study, 2 cases of non-serious rash occurred among 204 subjects. While these figures are lower than the 10 % frequency of the AE found in clinical trials with higher doses or longer treatment duration [6, 21], rash risk cannot be neglected in healthy subjects. The possibility of developing serious AEs should serve as evidence for not using higher doses in healthy volunteers due to safety and ethical reasons. However, lower

	AUC_{0-t}	AUC_{0-inf}	Cmax
T/R ratio	100.83	99.91	95.62
(90 % CI)	(92.53–107.88)	(93.79–108.40)	(90.91–100.57)
P-values (Schuirmann test)			
Inferior limit	<0.001	<0.001	<0.001
Superior limit	<0.001	<0.001	<0.001
Conclusion	Bioequivalence	Bioequivalence	Bioequivalence
CV (%)			
Intra-individual	14.4	15.3	10.0
Inter-individual	52.2	61.1	20.1
Power (%)	99.91	99.82	99.99

T/R = test/reference formulations. 90 % CI = 90 % Confidence Interval

Table 2 Bioequivalence evaluation of natural logarithm-transformed pharmacokinetic values of the studied formulation for 24 subjects after oral ingestion of lamotrigine 50 mg tablets.

doses (25 mg/day) may be difficult to measure with traditional laboratory methods in the range of pharmacokinetic study requirements.

A small percentage of patients switching AED preparations (from branded to generic or from generic to branded) may suffer from loss of seizure control [32]. These results emphasize the importance of bioequivalence testing of generic compounds, which, if possible, should be conducted in healthy volunteers. However, safety concerns associated with such studies should be minimized. Serious rash is thought to be dose-dependent, thus dose reduction to the minimum dose possible should help avoid its occurrence in most cases. Indeed, the FDA recommends lamotrigine bioequivalence studies with 50-mg doses [33]. In this study, we provided evidence showing the feasibility of this approach, as previous studies employed 100 mg [30]. Given that lamotrigine pharmacokinetics are linear (i.e., dose-independent), the bioequivalence of 25-, 100- and 200-mg tablets can be extrapolated from our results [20, 33].

In summary, the results of this study showed that the test lamotrigine formulation was bioequivalent to the reference product in healthy male subjects after oral administration of 50-mg dispersible tablets.

Conflict of interest

SPLL, LO and FM received honoraria for conducting this study. JJRM works for IVAX-TEVA, Argentina as medical advisor. PP is a former medical advisor of IVAX-TEVA, Argentina. This study was supported by IVAX-TEVA Argentina, a member of the TEVA Group.

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