

# Single-Dose, Randomized, Open-Label, Two-Way, Crossover Bioequivalence Study of Two Formulations of Pregabalin 300 mg Hard Capsules in Healthy Volunteers Under Fasting Conditions

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## Abstract

**Aims** This bioequivalence study was conducted to assess the bioequivalence of two formulations, test and reference, of pregabalin 300 mg hard capsules, under fasting conditions.

**Methods** This was a single-center, randomized, single-dose, open-label, laboratory-blinded, two-way crossover study, with a minimum washout period of 7 days. Plasma samples were collected prior to and up to 36 h after dosing. Pregabalin plasma concentrations were determined, using a validated method, by reversed phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (LC–MS–MS). Pharmacokinetic metrics used for bioequivalence assessment were the  $AUC_{(0-t)}$  (area under the plasma concentration–time curve from time zero to time of last observed non-zero plasma concentration) and the  $C_{max}$  (maximum observed plasma concentration). These parameters were determined from the pregabalin plasma concentration data using noncompartmental analysis.

**Results** Forty healthy subjects, age ranging from 18 to 43 years old, were enrolled and randomized, of whom 39 completed the study. The ratio of geometric least square means for  $C_{max}$  was 99.29 % (90 % confidence interval [CI] 93.29–105.67). The ratio of geometric least square means for  $AUC_{(0-t)}$  was 101.54 % (90 % CI

100.13–102.98). The 90 % CIs were within the predefined range (80.00–125.00).

**Conclusions** Bioequivalence between test and reference formulations, under fasting conditions, was concluded both in terms of rate and extent of absorption.

## 1 Introduction

Pregabalin, the (*S*)-3-(aminomethyl)-5-methylhexanoic acid (ATC N03AX16; CAS 148553-50-8), selectively binds with high affinity to the  $\alpha_2\delta$  subunit of voltage-gated calcium channels, widely distributed throughout the central and peripheral nervous systems. This modulates calcium influx in presynaptic nerve terminals to reduce excessive release of several excitatory neurotransmitters. Pregabalin is structurally related to the naturally occurring amino acids L-leucine and  $\gamma$ -aminobutyric acid (GABA) [1, 2]. Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults, adjunctive therapy in adults with partial seizures with or without secondary generalization, and treatment of generalized anxiety disorder (GAD) in adults. The dose range is 150–600 mg per day given in either two or three divided doses [1].

Pregabalin is absorbed rapidly (peak plasma concentrations occur within 1.5 h) after oral administration and exposure to single (25–300 mg/day) or multiple dosages (75–900 mg/day) is dose proportional. The oral bioavailability of pregabalin is high ( $\geq 90$  %) and independent of dose. The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in  $C_{max}$  (maximum observed plasma concentration) of approximately 25–30 % and an increase in  $t_{max}$  (time to maximum concentration) to approximately 3 h. However, administration of pregabalin with food has no clinically relevant effect on the total

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absorption of pregabalin. Therefore, pregabalin can be taken with or without food. Pregabalin does not bind to plasma proteins. The apparent volume of distribution following oral administration is approximately 0.5 L/kg. Metabolism of pregabalin is negligible with most of the drug excreted unchanged in the urine with a mean elimination half-life of 6.3 h in subjects with normal renal function. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance [1–4]. Pregabalin pharmacokinetics is linear over the recommended daily dose range [1–3]. According to the European guideline, two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance; that is, similarity in terms of safety and efficacy [5].

This study aimed to compare the rate and extent of absorption of a test formulation of pregabalin 300 mg and those of the European reference medicinal product (Lyrica®), administered as a 1 × 300 mg capsule under fasted conditions, a surrogate for therapeutic equivalence.

## 2 Volunteers and Methods

### 2.1 Study Protocol

An independent ethics committee approved the clinical study protocol and a letter of no-objection was obtained from the Canadian authorities on 5 May, 2011. The study was performed in accordance with the Helsinki Declaration [6] and Good Clinical Practice Guideline [7] and informed consent was obtained from participants prior to study commencement. The clinical part of the study was conducted at Algorithme Pharma Clinical Research Facility (Mount-Royal, QC, Canada) and the bioanalytical part at Anapharm Europe, SL facility (Barcelona, Spain). Pharmacokinetic and statistical analyses were also performed by Algorithme Pharma Inc. (Laval, QC, Canada).

### 2.2 Volunteers

Subjects were judged eligible for enrollment if they were in compliance with all the inclusion and exclusion criteria described in the protocol. Subjects included in this study were male, healthy, adult non-smokers or ex-smokers, aged  $\geq 18$  years and  $\leq 45$  years with body mass indices (BMI)  $\geq 22.0$  and  $< 30.0$  kg/m<sup>2</sup>. Clinically significant diseases were not captured in the medical history, and no evidence of clinically significant findings on physical examination

and/or clinical laboratory evaluations (hematology, biochemistry, ECG and urinalysis) was found. The following procedures were performed at screening: medical history, demographic data (including sex, age, race, body weight [kg], height [cm], and BMI [kg/m<sup>2</sup>]), vital signs measurements, 12-lead electrocardiogram (ECG), physical examination, urine ethanol and drugs of abuse screen, and clinical laboratory tests (hematology, biochemistry, urinalysis, human immunodeficiency virus [HIV], hepatitis C [HCV] antibodies, and hepatitis B surface antigen [HBsAg]).

The sample size was estimated from Algorithme's in-house data on intra-subject coefficients of variation (ISCVs) for AUC (area under the plasma concentration curve) and  $C_{\max}$ . Considering this information and an expected ratio of AUC and  $C_{\max}$  within 0.90 and 1.11, the study was expected to have a power of at least 80 % to show bioequivalence. Forty healthy male subjects were randomly assigned to test formulation or reference formulation in accordance with the randomization scheme previously generated using computerized software; 39/40 subjects completed the crossover design and were included in the pharmacokinetic and statistical analysis. The safety population included 40 subjects.

### 2.3 Drug Products

Pregabalin 300 mg hard capsule, manufactured by West Pharma, S.A. for Tecnimede, Sociedade Técnico-Medicinal S.A. (batch no. 11753, expiry date 30/09/2012) was compared with the Portuguese reference product, Lyrica® 300 mg hard capsule (batch no: 0332128P; expiry date 11/2011), manufactured by Pfizer GmbH (Germany) and acquired from a local pharmacy.

### 2.4 Study Design

The aim of this study was to compare the rate and extent of absorption of the test product of pregabalin 300 mg hard capsule (manufactured by West Pharma, S.A. for Tecnimede, Sociedade Técnico-Medicinal S.A., Sintra, Portugal) with the reference product, Lyrica® 300 mg hard capsule (manufactured by Pfizer GmbH, Germany), administered as a 1 × 300 mg capsule, under fasting conditions. This was a single-center, randomized, single-dose, laboratory-blinded, open-label, two-period, two-sequence, crossover bioequivalence study in healthy volunteers.

Subjects were assigned to one of two treatment sequences. No food was allowed from at least 10 h before dosing until at least 4 h after dosing, after which a standardized lunch was served. A supper and a light snack were also served at appropriate times thereafter, but not before 9 h after dosing. With the exception of the 240 mL of

water administered at the time of dosing, fluids were not permitted from 1 h before dosing to 1 h after dosing; water was permitted ad libitum at all other times.

The treatment periods were separated by a washout period of 7 days.

## 2.5 Randomization and Blinding

The order of investigational product administration was sequentially assigned from a computer-generated randomization scheme. The randomization scheme was kept unavailable to the bioanalytical division until completion of both the clinical and analytical phases.

## 2.6 Drug Analysis

Subjects were confined to the Algorithmme Pharma Clinical Research Facility from at least 10 h prior to drug administration until after the 36-h post-dose blood draw, in each period. Blood samples were collected in pre-cooled K2 EDTA (dipotassium ethylene diamine tetra-acetic acid) Vacutainers, prior to study drug administration and 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 3.00, 4.00, 6.00, 9.00, 12.0, 16.0, 24.0 and 36.0 h post-dose in each period. Within 110 min after blood collection, samples were centrifuged at a temperature of 4 °C nominal and at approximately 1900×g for 10 min. The plasma obtained was separated into duplicate polypropylene culture tubes, when feasible. The tubes were labeled with a code number that did not reveal treatment identity. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -20 °C nominal until sent on dry ice to the analytical facility for assay. The experimental samples were assayed for pregabalin using a validated chromatographic method with mass spectrometry detection (LC-MS/MS). The sample pretreatment required one-step preparation with the addition of methanol in order to promote protein precipitation; 900 µL of internal standard (IS) solution in methanol was added to 100 µL of plasma and vortexed for 60 s; 200 µL of the clear supernatant was transferred into vials and a 10 µL aliquot of each sample was injected into the LC-MS/MS system. Chromatographic separation was achieved through an Agilent Zorbax SB-C18 (50 × 4.6 mm, 3.5 µm) at room temperature. For the mobile phase, a mixture of methanol: 1 mM ammonium acetate (75:25, v/v) and 0.1 % of formic acid was used at a flow rate of 1 mL/min. Quantification was performed using a selected reaction monitoring (SRM) of the transitions  $m/z$  160.2 > 142.3 for pregabalin and  $m/z$  163.8 > 146.3 for IS.

The LC-MS/MS method for the quantification of pregabalin was specific and linear in the range of 30–15,000 ng/mL. A calibration curve was analyzed for each set of samples. The method showed good linearity

over the studied range ( $r \geq 0.9997$ ). The between-run accuracy ranged from 100.34 to 101.24 % and precision (expressed as the CV %) ranged between 1.66 and 5.35 %. The within-run accuracy ranged from 99.21 to 107.28 % and precision ranged from 1.22 to 6.25 %.

Analyses of drug concentrations were performed according to OECD (Organisation for Economic Co-operation and Development) good laboratory practice (GLP) standards and validation results were in accordance with the international requirements for bioanalytical methods, allowing the use of the method in the present bioequivalence study.

## 2.7 Pharmacokinetic Analysis

Pharmacokinetic analyses were performed using Kinetic software (version 9.01; Algorithmme Pharma Inc., Laval, Canada).

Individual and mean pregabalin plasma concentrations were plotted over the sampling period using untransformed and ln-transformed data. Only subjects with concentration data for both test drug product and reference drug product were included in the pharmacokinetic analysis. Drop-out subjects were not to be replaced. If a pre-dose concentration of pregabalin was detected, the subject's data could be included in the pharmacokinetic and statistical analysis, without adjustment, if it was  $\leq 5$  % of the  $C_{\max}$  value of the corresponding period. If it was  $> 5$  % of the  $C_{\max}$  value, the subject was to be dropped from all pharmacokinetic and statistical evaluations of pregabalin.

The following pharmacokinetic metrics were to be calculated: maximum observed plasma concentration ( $C_{\max}$ ), time of maximum measured plasma concentration ( $t_{\max}$ ), cumulative area under the plasma concentration time curve calculated from 0 to time of the last quantifiable concentration (tLQC) using the linear trapezoidal method ( $AUC_{(0-t)}$ ), extrapolated area under the plasma concentration time curve to infinity ( $AUC_{(0-\infty)}$ ), apparent elimination rate constant estimated from a non-linear least-squares regression model ( $K_{el}$ ) and half-life of elimination ( $t_{1/2el}$ ).

The main absorption and disposition parameters were to be estimated using a noncompartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was to be used to estimate the area under the curve and the terminal phase was to be estimated by maximizing the coefficient of determination estimated from the log-linear regression model. However, they were not to be estimated for individual concentration-time profiles where the terminal log-linear phase could not be reliably characterized.

The mean, medium, minimal value, standard deviation and coefficient of variation were to be calculated for plasma concentrations at each individual time point and for all pharmacokinetic parameters.

## 2.8 Statistical Analysis

Statistical analyses were generated with SAS<sup>®</sup> software (version 9, SAS Institute Inc., Cary, NC, USA) using the GLM (general linear model) procedure.

The assessment of bioequivalence was based upon 90 % confidence intervals for the ratio of the population geometric means for  $AUC_{(0-t)}$  and  $C_{max}$  obtained after test and reference drug product dosing. The natural logarithmic transformation of  $C_{max}$ ,  $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$  were used for statistical inference. The parameter  $t_{max}$  was analyzed using a nonparametric approach. The evaluation of fixed period, sequence and treatment effects were based on the Wilcoxon's rank sum test (Mann–Whitney  $U$  test).

The other untransformed and In-transformed pharmacokinetic variables were analyzed using an analysis of variance (ANOVA) model. The fixed factors included in this model were the subject effect (nested within sequence), the treatment received, the period at which it was given and the sequence in which each treatment was being received.

The sequence, period and treatment effects were to be assessed at the 5 % two-sided level. Furthermore, the 90 % confidence interval for the exponential of the difference in least square (LS) means between the test drug product and the reference drug product was to be calculated for the In-transformed parameters (test to reference ratio of geometric LS means). Bioequivalence assessment was to be based on the 80.00–125.00 % range.

The formula to estimate the intra-subject coefficient of variation was:  $\sqrt{e^{MSE} - 1}$ , where MSE is the mean square error obtained from the ANOVA model of the In-transformed parameters. If a pharmacokinetic metric could have not been determined for one period in a subject, the corresponding subject was to be excluded for the particular statistical comparison.

The intra-subject variation following a single dose of pregabalin could be as high as 19 % for  $C_{max}$  and 6 % for  $AUC_{(0-t)}$ . Statistically, given that the expected test to reference ratio of geometric LS means should fall within 90 and 111 %, it was estimated that the lowest number of subjects to meet the 80.00 to 125.00 % bioequivalence range with a statistical a priori power of at least 80 % was about 34.

Therefore, the inclusion of 40 subjects was estimated to be sufficient to also take into account the possibility of drop-outs, variations around the estimated ISCV, and to conclude in favor of the hypothesis of bioequivalence with sufficient statistical power.

## 2.9 Tolerability Analysis

Adverse events (AEs) were listed and coded using Medical Dictionary for Regulatory Activities (MedDRA), version

14.0. Adverse events were summarized descriptively in the safety population, and were tabulated by treatment group, system organ class (SOC), preferred term (PT), causality, and severity.

## 3 Results

### 3.1 Pharmacokinetic and Statistical Analysis

Forty male healthy volunteers were enrolled and randomized. One subject dropped out and 39 completed both periods of the study. Pharmacokinetic and statistical analysis included 39 volunteers. The disposition of the subjects is presented in Fig. 1. The pharmacokinetic metrics were not adjusted for differences in assayed content of the test and reference drug product batch. A summary of the pharmacokinetic metrics obtained for test drug product and reference drug product is presented in Table 1.

The mean  $C_{max}$  were, respectively, 7375.91 and 7420.08 ng/mL for the test and reference. The ratio of geometric LS means was 99.29 % (90 % confidence interval [CI] 93.29–105.67). The mean  $AUC_{(0-t)}$  were, respectively, 54,808.13 and 53,959.26 ng·h/mL for test and reference. The ratio of geometric LS means was 101.54 % (90 % CI 100.13–102.98). Both ratios of geometric LS means and 90 % CI were within the prespecified bioequivalence range (80.00–125.00). The mean  $AUC_{(0-\infty)}$  were, respectively, 56,132.73 and 55,236.37 ng·h/mL for the test and reference. The ratio of geometric LS means was 101.59 % (90 % CI 100.06–103.14). The median  $t_{max}$  were 1.03 and 1.25 h for the test and reference, respectively. The mean  $K_{el}$  were 0.1071 and 0.1068 h<sup>-1</sup> for the test and reference, respectively. Finally, the mean  $t_{1/2el}$  were 6.47 and 6.49 h, for the test and the reference, respectively.

The mean of the individual ratio of  $AUC_{(0-t)}$  over  $AUC_{(0-\infty)}$  ( $AUC_{(0-t)}/AUC_{(0-\infty)}$ ) were 97.64 and 97.69 % for the test and reference, respectively. The ISCV was 16.4 and 3.7 % for  $C_{max}$  and  $AUC_{(0-t)}$ , respectively.

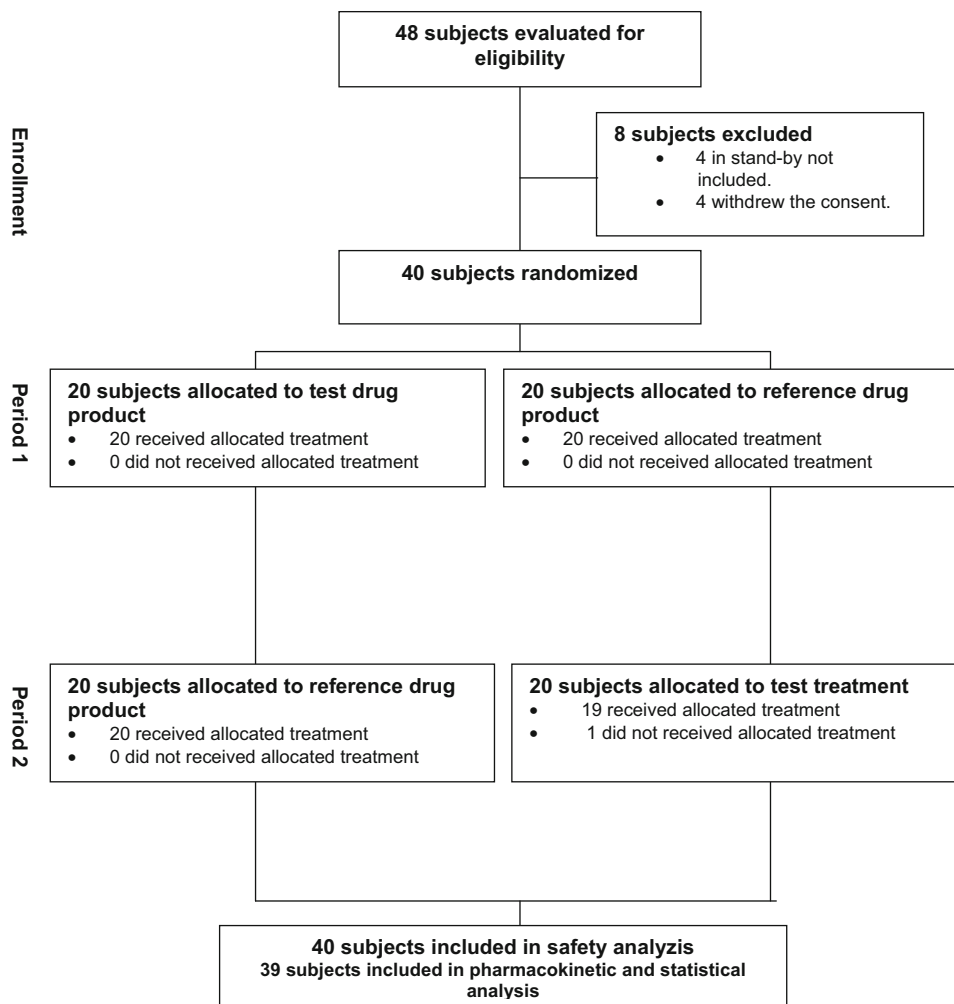
The mean measured plasma concentration versus time profile obtained after the administration of the test and reference is depicted in Fig. 2.

The parameter  $t_{max}$  was analyzed using a non-parametric approach. The  $F$ -value for treatment was 0.10 and the  $p$  value was not significant ( $p = 0.92115$ ).

### 3.2 Tolerability Analysis

Thirty-six of the 40 (90 %) subjects included in this study experienced a total of 158 AEs. Thirty-one (79.5 %) subjects reported 67 AEs, corresponding to five different SOCs and 13 different PTs, after the single-dose administration of the test product, and 35 (87.5 %) subjects reported 91 AEs

**Fig. 1** Disposition of subjects. Test drug product = Sociedade Técnico Medicinal—S.A., Portugal, pregabalin 1 × 300 mg hard capsule. Reference drug product = Pfizer GmbH, Germany (Lyrica®), pregabalin 1 × 300 mg hard capsule



**Table 1** Pharmacokinetic variables (mean and coefficient of variation [CV]) for test and reference drug product

Variable	Test drug product		Reference drug product	
	Geometric mean	CV (%)	Geometric mean	CV (%)
$C_{max}$ (ng/mL)	7375.91	24.9	7420.08	26.5
$t_{max}$ (h) <sup>a</sup>	1.03	51.8	1.25	42.3
$AUC_{(0-t)}$ (ng·h/mL)	54,808.13	12.8	53,959.26	14.0
$AUC_{(0-\infty)}$ (ng·h/mL)	56,132.73	13.4	55,236.37	14.5
$AUC_{(0-t)/(0-\infty)}$ (%)	97.64	1.2	97.69	1.1
$K_{el}$ (h <sup>-1</sup> )	0.1071	12.7	0.1068	12.6
$t_{1/2el}$ (h)	6.47	12.1	6.49	12.1

$AUC_{(0-\infty)}$  area under the plasma concentration time curve to infinity,  $AUC_{(0-t)}$  area under the plasma concentration–time curve from time zero to time of last observed non-zero plasma concentration,  $C_{max}$  maximum observed plasma concentration,  $K_{el}$  apparent elimination rate constant estimated from a non-linear least-squares regression model,  $t_{1/2el}$  half-life of elimination,  $t_{max}$  time of maximum measured plasma concentration

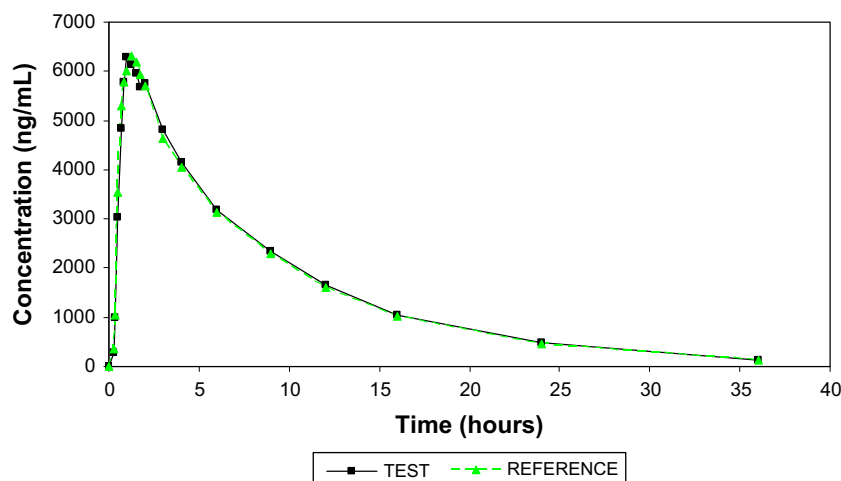
<sup>a</sup> Median is presented for  $t_{max}$

(seven different SOC and 22 different PTs) after the single-dose administration of the reference product. The intensity of AEs ranged from mild to severe, and one AE (dizziness) had no assigned degree of severity. Five severe

AEs (fatigue, headache, somnolence [two occurrences] following test, and somnolence following reference) were observed during the study. None of the AEs judged to be related to the investigational products were unexpected. No



**Fig. 2** Mean concentration versus time curve—pregabalin



serious AEs or deaths were reported during this study. One (2.5 %) subject took a concomitant medication during the study. No subject was withdrawn from the study for safety reasons.

#### 4 Discussion

Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults, adjunctive therapy in adults with partial seizures with or without secondary generalization, and treatment of GAD in adults [3]. The absorption is rapid (peak plasma concentrations occur within 1.5 h) after oral administration and exposure to single (25–300 mg/day) or multiple dosages (75–900 mg/day) is dose proportional and oral bioavailability is high ( $\geq 90$  %) and independent of dose [1].

Pregabalin is a Biopharmaceutical Classification System (BCS) Class I compound (highly permeable and highly soluble) [10]. Additionally, pregabalin does not have a narrow therapeutic index and the formulations were not modified release. Taking these in consideration, the concept of biowaiver based on BCS should be considered as a surrogate for in vivo bioequivalence [5]. A generic medicinal product is considered bioequivalent to a reference medicinal product when the 90 % confidence interval around the estimated ratio of geometric means (GMR) of AUC and  $C_{\max}$  is between 0.80 and 1.25. As per regulatory and scientific requirements, when a generic medicinal product and a reference medicinal product are compared, a single-dose crossover design is recommended [5].

The treatment periods should be separated by a washout period of at least 5 elimination half-lives in order to guarantee that the drug concentrations are below the lower limit of bioanalytical quantification (LOQ) in all subjects at the beginning of each period [5].

In this study, the treatment periods were separated by a washout period of 7 days to ensure that no carry-over effect is observed, corresponding to more than 10 times the expected half-life of the measured moiety [5].

The means of the individual ratio of  $AUC_{(0-t)}$  over  $AUC_{(0-\infty)}$  ( $AUC_{(0-t)}/AUC_{(0-\infty)}$ ) were 97.64 and 97.69 %, respectively, for the test drug product and reference drug product. This implies that the blood sampling schedule was defined adequately to characterize at least 80 % of the area under the curve for both products [5].

Other authors conducted bioequivalence studies of pregabalin with different washout periods and blood sampling schedules [8, 9].

The intra-subject variability reflects the residual variability observed in the pharmacokinetic metrics after accounting for possible differences between sequence, period, and formulation effects as well as accounting for between-subject variations. The intra-subject coefficient of variation was 16.4 and 3.7 % for  $C_{\max}$  and  $AUC_{(0-t)}$ , respectively.

All AEs reported for subjects included in the statistical analysis were considered to have no impact on the pharmacokinetic profiles of the drugs and the assessment of bioequivalence. During the study, five severe AEs were observed: four occurrences after test administration—fatigue, headache and somnolence (two occurrences), and one after reference administration—somnolence. None of the AEs judged related to the investigational product were considered unexpected, and, generally the drugs were considered safe and well tolerated.

#### 5 Conclusions

The results presented herein show that the criteria used to assess bioequivalence between the test and reference formulations were all fulfilled. The test to reference ratios of

**Table 2** 90 % Confidence intervals (CIs) for  $C_{\max}$  and  $AUC_{(0-t)}$ 

Variable	ISCV (%)	Geometric least square mean <sup>a</sup>		Ratio <i>T/R</i> (%)	90 % CI
		Test	Reference		
$C_{\max}$	16.4	7377.67	7430.57	99.29	93.29–105.67
$AUC_{(0-t)}$	3.7	54,818.39	53,984.39	101.54	100.13–102.98

$AUC_{(0-t)}$  area under the plasma concentration–time curve from time zero to time of last observed non-zero plasma concentration,  $C_{\max}$  maximum observed plasma concentration, *ISCV* intra-subject coefficient of variability, *T/R* test/reference

<sup>a</sup> Units are ng/mL for  $C_{\max}$  and ng·h/mL for  $AUC_{(0-t)}$

geometric LS means and corresponding 90 % confidence intervals for  $C_{\max}$  and  $AUC_{(0-t)}$  were all within the acceptance range of 80.00–125.00 % as depicted in Table 2.

Therefore, it can be concluded that the test formulation (pregabalin 300 mg hard capsules, West Pharma S.A., Portugal for Tecnimede S.A., Portugal) is bioequivalent to the reference formulation (Lyrica<sup>®</sup> 300 mg hard capsules, Pfizer GmbH, Germany) following a 1 × 300 mg dose under fasting conditions.

**Conflict of interest** Tecnimede is the Sponsor of this study. Augusto Filipe, Pedro Pedrosa, Susana Almeida, Rita Neves and Susana Marques are employees of the Sponsor of this study. Eric Sicard and Julie Massicotte are employees of the Clinical Contract Research Organization contracted to perform this study. Jordi Ortuño is employee of the Analytical Laboratory contracted to perform the assays for this study.

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