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A Bioequivalence Study of two Formulations of Lacosamide

Dario Zava*

Medical-Scientific Director, Istituto Lusofarmaco D'Italia Institute of Italy, Milanofiori - Street 6 - Building L, 20089 Rozzano, Italy

***Corresponding Author:** Dario Zava, Medical-Scientific Director, Istituto Lusofarmaco D'Italia Institute of Italy, Milanofiori - Street 6 - Building L, 20089 Rozzano, Italy, Tel: +39/(0)2 516555236; +39/348 3101700, E-mail: dzava@lusofarmaco.it

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Abstract

This study was conducted to compare the bioavailability of two tablet formulations containing 200 mg Lacosamide (one Lacosamide 200 mg film-coated tablet marketed in Italy as Ollat®, one Vimpat® coated tablet).

20 healthy subjects were enrolled in a single-center, randomized, single-dose, laboratory-blinded, 2-period, 2-sequence, crossover study, with a minimum washout period of 7 days. All the 20 subjects completed the study. Plasma samples were collected up to 72.0 hours post-dosing. Lacosamide levels were determined using a validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) method. Pharmacokinetic parameters used for bioequivalence assessment trough a non-compartmental analysis were: area under the plasma concentration-time curve from time zero to time t (AUC_{0-t}) and maximum observed plasmatic concentration (C_{max}). The 90% confidence intervals obtained by analysis of variance resulted within the predefined ranges: 98.60 – 107.06% for C_{max} (Test to Reference ratio of geometric Least Square (LS) means 102,7%) and 99.11 – 103.03% for AUC_{0-t} (Test to Reference ratio of geometric LS means 101.5%). Bioequivalence between formulations was achieved considering both rate and extent of absorption.

Keywords: Bioavailability; Bioequivalence; Lacosamide; Pharmacokinetics; Tablet.

List of Abbreviations

AED: Antiepileptic Drug; ANOVA: Analysis of Variance, AUC: Area Under the plasma concentration-time Curve, $AUC_{0-\infty}$: Area Under the plasma concentration-time Curve from time zero to infinity, AUC_{0-t} : Area Under the plasma concentration-time Curve from time zero to time t, CFR: Code of Federal Regulations, C_{max}: Maximum Plasmatic Concentration, CRMP-2: Collapsin Response Mediator Protein 2, EDTA: Ethylenediaminetetraacetic Acid, EU: European Union, GCP: Good Clinical Practice, GLP: Good Laboratory Practice, HPLC: High-Performance Liquid Chromatography, ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, LS: Least Square, MS/MS: Tandem Mass Spectrometry, MSE: Mean Square Error, OECD: Organization for Economic Cooperation and Development, PK: Pharmacokinetics, QA: Quality Assurance, QC: Quality Control, T_{half}: Mean elimination half-life, T_{max}: Time to

peak drug concentration, US: United States, VGSC: Voltage Gated Sodium Channel

Introduction

Antiepileptic drugs (AEDs) are the mainstay of treatment for patients with epilepsy [1]. However, despite the number of AEDs available for the treatment of focal-onset seizures (previously termed partial-onset seizures [2], treatment resistance occurs in approximately one third of patients [3] and achieving seizure control whilst avoiding unnecessary adverse events continues to be a major challenge [4]. Newer AEDs have novel mechanisms of action designed to decrease drug–drug interactions and achieve seizure freedom [5].

Among currently available AEDs is the functionalized amino acid Lacosamide. It is a well-established option for the treatment of focal-onset seizures in adults and adolescents in the EU and the USA [6,7] and has recently been approved for use in children aged 2 years and older [8,9].

Lacosamide is generally effective and well tolerated to use in children from 2 years of age with epilepsy both in monotherapy and as adjunctive treatment of partial-onset seizures with or without secondary generalisation. Indeed Lacosamide is effective and safe in the treatment of primary generalised tonic-clonic seizures in children from 4 years of age with idiopathic generalised epilepsy [8,9].

Lacosamide works mainly by enhancing the inactivation of slow sodium channels. Indeed, Lacosamide exerts its anticonvulsant effects through two novel mechanisms of action.The first is through its enhancement of slow inactivation of voltage gated sodium channels (VGSCs). Depolarization of VGSCs allows sodium ion influx across neuronal cell membranes, an important step in the initiation of the action potential. After depolarization, VGSCs enter an inactivated state before reverting back to their resting state (where they are available for depolarization again). During the inactivated state, VGSCs are unavailable for depolarization. This fast, inactivated state is milliseconds long and is the site of action of the traditional sodium-channel blockers. In conditions of sustained depolarization and repetitive firing such as epilepsy, VGSCs can undergo a conformational change into the slow inactivation state, which is seconds long. Lacosamide enhances this transition of VGSCs into the slow inactivated state, reducing the availability of VGSCs for depolarization and subsequent neuronal firing [11].

This is a novel mechanism of action, as traditional AEDs act on inactivation of fast sodium channels; thus, Lacosamide selectively affects pathological currents caused by slow channels versus inactivation of fast channels, which occurs in normally functioning neurons. This prevents activation of synaptic currents, thereby preventing the propagation of pathological currents and stabilising the neural network [10].

The second potential mechanism of action is Lacosamide's binding to collapsin response mediator protein 2 (CRMP-2), which is involved in neuronal differentiation, polarization, and axonal outgrowth [12].

Lacosamide has linear kinetics and reaches peak concentrations in plasma in one to four hours; its half-life is 13 hours, allowing for twice-daily dosing [10]. Lacosamide is eliminated by renal clearance and does not interact with the P450 system, hence limiting its interaction with the metabolism of other drugs [13]. No pharmacodynamic interactions with Lacosamide are known. In clinical practice, Lacosamide monotherapy is started at 100 or 200 mg a day in divided doses, to a maximum of 600 mg a day until seizure freedom or reduction in seizure frequency is achieved, while Lacosamide in combination therapy is started at 100 mg a day in divided doses, to a maximum of 400 mg a day [8].

Material and Methods

Lacosamide

Despite the availability of numerous antiepileptic drugs (AEDs) and the continuing emergence of novel AEDs, 30% of patients with epilepsy still suffer from uncontrolled seizures and many experience unpleasant adverse effects [2]. Lacosamide is a novel antiepileptic drug (AED) and its mechanism of action distinguishes it from other AEDs. Unlike most of classical AEDs which affect fast inactivation, Lacosamide enhances sodium channel slow inactivation. This results in stabilization of neuronal membranes and decrease in neuronal firing [10]. It has been suggested that the drug also binds to collapsin response mediator protein 2 (CRMP-2) which plays a role in neuronal differentiation [12].Lacosamide has a good pharmacokinetic and pharmacodynamic profile with low risk of pharmacokinetic interactions and well absorbtion [10-13].

Lacosamide fulfills all the properties to be a first choice option for the treatment of seizures both in monotherapy and in combination wth other AEDs [5-7].

Population

Twenty volunteers of both genders (9 female and 11 male subjects) aged between 18 and 55 years were screened for the study. All volunteers were considered as being eligible to participate in the study and fulfilled all the inclusion and none of the exclusion criteria defined in the study protocol. All volunteers showed good health conditions and the absence of significant disease after assessment of medical history, verification of vital signs, physical examination, electrocardiogram, and routine laboratory tests.

The protocol and the informed consent were approved by an institutional review board (Health Canada) on May 18, 2016. Guidelines as drawn up by the institutional review board were followed with regard to the treatment of human subjects in the study. This study was conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the Food & Drug Administration (FDA) GCP Code of Federal Regulations (CFR) Title 21 (part 56), the Directive 2001/20/EC (Europe), the Tri-Council Policy Statement (Canada) and the GCP.

After explaining the nature and purpose of the study, all volunteers provided their written informed consent for participation.

Study Treatment

The following investigational products were administered under fasting conditions:

Test, one Lacosamide 200 mg film coated-tablet manufactured by Combino Pharm (Malta) Ltd., Malta (this product will be marketed in Italy with the brand name Ollat®) and Reference, one Vimpat® 200 mg film-coated tablet, manufactured by Aesica Pharmaceuticals GmbH, Germany, sourced from German market.

The products were to be administered to the 20 healthy male and female Caucasian subjects according to the following design: Sequence 1 (n=10) Period 1/Test- Period 2/Reference; Sequence 2 (n=10) Period 1/Reference – Period 2/Test.

Test Batch Treatment N° was: 16FF202A and expiry date (08/2016) manufacturer Combino Pharm (Malta) Ltd., Malta.

Reference Batch treatment N° was: 92290 (Blister)/9229006 (Box) expiry date 03/2020 manufacturer Aesica Pharmaceuticals GmbH, Germany.

Study Design

This was a randomized, single-dose, laboratory-blinded, 2-period, 2-sequence, crossover, single-center study in healthy White male and female subjects.

In each period subjects were asked to arrive at the clinical site at least 10 hours before dosing. After a supervised overnight fasting, a single 200 mg oral dose of the assigned formulation was administered in the morning. Subjects were allowed to leave the clinical site after the 24-hour postdose blood draw and were asked to return to the clinical site before each of the 3 remaining blood samples. The wash-out period was 7 calendar days.

In each study period, 22 blood samples were collected. The first blood sample was collected prior to drug administration while the others were collected up to 72 hours after the drug administration each in one tube of 4 mL (K2 EDTA Vacutainers).

This sampling was planned in order to provide a reliable estimate of the extent of absorption as well as the terminal half-life. Samples were processed and stored under conditions that have been shown not to cause significant degradation of the analyte. To ensure that no carry-over effect is observed, a wash-out of 7 calendar days was inserted between drug administrations, corresponding to more than 10 times the expected half-life of the moiety to be measured.

Blood samples for pharmacokinetic measurements were collected prior to drug administration and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, and 72.00 hours following drug administration.

Blood samples were collected in K2 EDTA Vacutainers. Collected blood samples were kept in an ice/water bath. As soon as possible following blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500*g* for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes, when feasible. The tubes were labeled with a code number that did not reveal formulation 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 bioanalytical facility for assay. The time from blood sample collection to plasma aliquot storage should have been within 90 minutes.

Plasma samples were received frozen by Sponsor’s analytical facility.

Method of Measurement

The experimental samples were assayed for Lacosamide at the Sponsor’s analytical facility using a validated High-performance liquid chromatography (HPLC) method with tandem mass spectro-

metry (MS/MS) detection. The lower limit of quantitation and upper limit of quantitation were 50.0 and 10000.0 ng/mL, respectively.

Designated personnel from the Sponsor were responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the trial was conducted and data was generated, documented and reported in compliance with the protocol, ICH Guideline E6 for Good Clinical Practices, applicable requirements as outlined in the Food & Drug Administration (FDA) and Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (GLP), and the Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010).

Pharmacokinetic and Statistical Analysis

This study was to be conducted in adherence to the Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1, 2010).

Samples from all subjects who received at least one of the investigational products were to be assayed.

Subjects who provided evaluable data for both Test and Reference products were to be included in the pharmacokinetic and statistical analysis. Concentration data of the remaining subjects were to be presented separately.

Subjects who did not complete the sampling schedule of one or more study periods may have been included in the statistical and pharmacokinetic analysis and bioequivalence determination for only the pharmacokinetic (PK) parameters that were judged not to be affected by the missing sample(s) as long as these data were available for both treatments, i.e., Test and Reference. This decision was to be documented by the SRA department and approved by the sponsor before the start of the sample analysis by the bioanalytical facility.

Lacosamide plasma concentrations produced by the administration of the studied formulations were to be determined in order to establish the pharmacokinetic profile of the Test product in relation to the Reference product. Below limit of quantitation concentrations (coded BLQ) were to be treated as zero for all statistical analyses. All reported sampling time deviations from the schedule sampling time of 2 minutes or more were to be taken into consideration for evaluation of PK parameters.

In the case where concentrations of Lacosamide could not be determined due to bioanalytical or clinical reasons, these values were to be set to missing for the statistical and pharmacokinetic analysis.

In the case where less than 3 consecutive measurable concentrations of Lacosamide were observed, the AUC parameters were not to be estimated for that specific study period.

If a pre-dose concentration of Lacosamide was detected, the subject's data could have been included in the pharmacokinetic and statistical analysis without adjustment, if the pre-dose concentration was equal to or less than 5% of the C_{max} value of the corresponding period. If the pre-dose concentration was greater than 5% of the C_{max} value, the subject was to be dropped from all pharmacokinetic and statistical evaluations.

In cases when no measurable concentrations or only very low plasma concentrations were observed for the Reference medicinal product (i.e. AUC_{0-T} was less than 5% of Reference medicinal product geometric mean AUC_{0-T} , which should be calculated without inclusion of data from the outlying subject), such subjects were to be excluded from the pharmacokinetic and statistical evaluation.

The main pharmacokinetic parameters of interest for this study were to be C_{max} and AUC_{0-T}. Other parameters such as T_{max}, $AUC_{0-\infty}$, residual area, λ_Z and T_{half} were to be provided for information purposes only.

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

Descriptive statistics were to be calculated for plasma concentrations at each individual time point and for all pharmacokinetic parameters. The individual plasma concentration/time profiles were to be presented using the actual sampling times whereas the mean plasma concentration/time profiles were to be presented using the theoretical sampling times.

Descriptive statistics were to be used to summarize adverse events, safety results and demographic variables (age, height, weight, and body mass index).

The natural logarithmic transformation of C_{max}, AUC_{0-T} and $AUC_{0-\infty}$was to be used for all statistical inference.

The parameter Tmax was to be analyzed using a non-parametric approach. Test of fixed period, sequence and treatment effects were to be based on the Wilcoxon's rank sum test (Mann-Whitney U-test). When appropriate (e.g. small or sparse sample), the exact version of the test was also to be presented. All other pharmacokinetic parameters were to be statistically analyzed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model were to be the subject effect (nested within sequence), the treatment received, the period at which it was given, as well as the sequence in which each treatment was received.

477266083312000The 90% confidence interval for the exponential of the difference in Least Square (LS) means between the Test and Reference product was to be calculated for the ln-transformed parameters (Test to Reference ratio of geometric LS means).

The formula to estimate the intra-subject coefficient of variation was to be: $\sqrt{e^{MSE}-1}$, where MSE is the Mean Square Error obtained from the ANOVA model of the ln-transformed parameters. In the event that the study was conducted in two or more groups and those groups were dosed at different clinical sites, or at the same site but greatly separated in time (months apart, for example), the statistical model was to be modified accordingly to incorporate the group effect. The fixed factors included in the modified model were to be the study group, the treatment received, the period at which it was given, the sequence in which each treatment was received, the subject effect (nested within the group-by-sequence interaction), the group-by-sequence interaction, as well as the group-by-treatment interaction whenever statistically significant at two-sided 5% level.

If a pharmacokinetic parameter could not be determined for one period in a subject, the corresponding subject was to be excluded from that particular statistical comparison.

Determination of Sample Size

The intra-subject variation following a single dose of Lacosamide appeared to be around 13% for Cmax and AUC0-T. Statistically, given that the expected Test to Reference ratio of geometric LS means should fall within 95 and 105%, it was estimated that the lowest number of subjects to meet the 80 to 125% bioequivalence range with a statistical a priori power of at least 90% was about 12.

However, since this was a pivotal study, which required that the study be finished with a minimum of 12 subjects, a sample size of 20 subjects was recommended and deemed sufficient to account for the possibility of drop-outs, variations around the estimated intra-subject CV and to conclude in favour of the hypothesis of bioequivalence with sufficient statistical power.

Results

All the 20 participant volunteers (9 females and 11 males) completed the study. The volunteers had mean age of 39 years, ranging from 24 to 54 years; mean weight of 70.3 kg (47.7 to 88.0 kg); mean height of 1.66 m (1.49 to 1.84 cm) and mean BMI of 25.4 kg/m^2 (21.3 to 29.5 kg/m^2). Lacosamide was well tolerated at the administered dose. No serious adverse events were seen or reported, and no pregnancies were detected. The mean curves for plasma concentration vs time obtained for test and reference drugs are shown in Figure 1. The curves are overlapped, showing a similar pharmacokinetic profile between the two drugs.

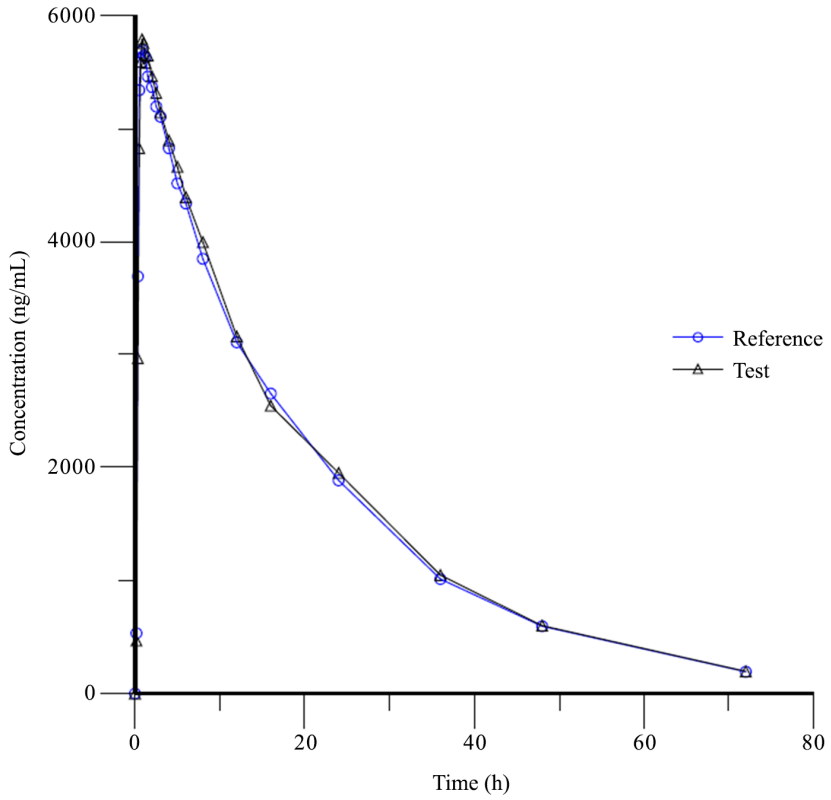

Figure 1: Plasma Linear Profile of the Mean for Lacosamide (n=20)

Table 1 shows the main study results and Table 2 shows the comparison of results with standards for bioequivalence. The mean elimination half-life (Thalf) was 14.33 (CV 22.6%) for Test and 14.42 (CV 19.4%) for Reference, p=NS. The lnAUC0- was 11.69 (CV 19%) for Test and 11.68 (CV 1.8%) for Reference p = NS.

Parameter	Test(N=20)		Reference(N=20)		*P**
	MEAN	C.V. (%)	MEAN	C.V. (%)	
C_{max} (ng/mL)	6294.2	(20.6)	6152.9	(22.4)	N.S.
ln (C_{max})	8.7280	(2.3)	8.7009	(2.6)	N.S
T_{max} (hours) $^{\$}$	0.83	(0.33-4.00)	0.92	(0.33-3.00)	N.S
AUC_{0-t} (ngh/mL)	118539.2	(20.2)	116994.4	(18.5)	N.S
ln (AUC_{0-T})	11.6626	(1.8)	11.6521	(1.7)	N.S
AUC_{0-} (ngh/mL)	123230.5	(21.5)	121576.0	(19.5)	N.S
ln (AUC_{0-})	11.6987	(1.9)	11.6887	(1.8)	N.S
Residual Area (%)	3.52	(66.7)	3.57	(56.1)	<0.10
λ_z (hours^{-1})	0.0505	(20.6)	0.0498	(19.2)	N.S
T_{half} (hours)	14.33	(22.6)	14.42	(19.4)	N.S

Table 1: Summary of Plasma Lacosamide Pharmacokinetic Parameters

*N:S: Not Significant whenever *p*-value <0.05$^{\$}$ For T_{max}, the median is presented and the statistical analysis is based on a rank-transformation

Parameter	Intrasubject Cv (%)	Geometric Ls Means*		Ratio (%)	90% Confidence Limits (%)	
		TEST (n=20)	REFERENCE (n=20)		LOWER	UPPER
C_{max}	7.5	6173.1	6008.3	102.74	98.60	107.06
AUC_{0-t}	3.5	116139	114930.4	101.5	99.11	103.03

Table 2: Comparison of Results with Standards for Bioequivalence

*Units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

Discussion

A two-period, two-sequence crossover design was considered as the design of choice for the two formulations comparison, taking into account the European bioequivalence guideline [14] and the pharmacokinetic profile of Lacosamide (15-17]. Lacosamide is approved in Europe in the 50, 100, 150 and 200 mg formulations as film-coated tablets. The 200 mg formulation was selected to test for bioequivalence. Both male and female volunteers were included in the study sample as, for this drug, no specific pharmacokinetic gender effects are known [15,17].

Healthy subjects were used, minimizing variability and thus allowing for a better comparison between the pharmaceutical products [14]. A minimum 7-day washout period was set, based on literature T1/2 of 13 hours [15-17], corresponding to more than 10 times the expected half-life of the moiety, allowing proper elimination of the drug administered in the first period. The sampling schedule over 72 hours was considered enough to allow a full characterization of the plasma profiles.

Results showed in Table 2 clearly demonstrate that the 90% confidence interval of the Cmax and AUCo-t geometric LS means of the Test to Reference formulation are within the pre-specified 80 and 125% bioequivalence range [14].

Lacosamide pharmacokinetic data seems to be in line with published data.

Conclusion

This bioequivalence study was well designed, demonstrating bioequivalence between one Lacosamide film-coated tablet marketed in Italy as Ollat® and one Vimpat® coated tablet (European reference formulation), in terms of both rate and extent of absorption. 90% confidence intervals of the main pharmacokinetic parameters, Cmax and AUC0-T comply with the 80 and 125 % acceptance interval.

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