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Research Article

# Bioequivalence Study of Two Linezolid 600 mg Immediate-release Oral Tablets in a Healthy Mexican Population under Fasting Conditions

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## ABSTRACT

**Objective:** To share pharmacokinetic data and a bio-analytical method developed for the conduction of a bioequivalence trial of Linezolid 600-mg tablets in Mexican population

**Methods:** Thirteen female and 13 male healthy volunteers were administered with a single oral dose of one 600-mg Linezolid tablet under fasting conditions, in a double-blinded cross-over design study, with blood sampling up to 24 h post-dose. Linezolid was measured by tandem Mass Spectrometry coupled to Ultra-Performance Liquid Chromatography (UPLC-MS/MS) with a validated method. Logarithmic ratios of maximal plasma Concentration ($C_{max}$) and Area under the Curve ($AUC_{0\text{-}24h}$) were used to establish 90% Confidence Intervals [CI] for bioequivalence.

**Results:** Both formulations (Zyvoxam™, Pfizer as reference product, and LINEZOLID generic formulation as test product) were safe and well tolerated. The analytical method proved to be linear with accuracy and precision within a range of 0.1-20 µg/mL; 90% CI for $C_{max}$ and $AUC_{0\text{-}24h}$ were [91.94–116.14] and [97.38–110.95], respectively, with a statistical power greater than 0.9. $C_{max}$ was reached at approximately 1 h, and plasma elimination half-life ($t_{1/2}$) was around 3.29 h for both products.

**Conclusion:** Assayed products met the criteria established by the Mexican regulatory agency (COFEPRIS) to be declared bioequivalent. Apparently, Mexican population appears to be a high absorber/ fast metabolizer of Linezolid, exhibiting a shorter $t_{1/2}$ and a reduced total amount of drug absorbed, compared to other non-Latin populations previously reported.

**Keywords:** Linezolid; Bioequivalence; Hospital-acquired pneumonia

## INTRODUCTION

Linezolid (LIN), that is, (N-{[(5S)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-2-oxo-1,3-oxazolidin-5-yl] methyl} acetamide (CAS No. 165800-03-3) is, to our knowledge, the first synthetic antibiotic of the oxazolidinone family. It is a small molecule (337.34 g/mol) with high water solubility (1.44 mg/mL, log P = 0.61) and a basic behaviour [1]. Due to these properties, LIN is formulated as oral tablets as well as parenteral solutions, corresponding to biopharmaceutical class I (high solubility, high permeability).

LIN is fast and hugely absorbed after an oral administration. Maximal plasma concentration is observed in the first 2 h post-dose. Absolute oral bioavailability of LIN is close to 100%, and it is not affected by food. Volume of distribution is around 40-50 L during steady state in health adult persons, with a plasma protein binding of 31%. The concentration ratio of LIN in alveolar liquid with respect to plasma is 4.5:1 at $C_{max}$. During its biotransformation, LIN is metabolized by opening and oxidation of the morpholinic ring by unspecific estearases, yielding the hydroxy-glycine metabolite, the most abundant and inactive entity. LIN is predominantly excreted by urine, with 40% as hydroxy-glycine metabolite, 30% as unaltered LIN, and the remainder as minor metabolites. Reported plasma elimination half-life is between 5 and 7 h, which is prolonged during renal impairment; hepatic dysfunction does not modify the pharmacokinetics of LIN [2].

LIN has a racemic structure, but only the (S)-enantiomer possesses the antibiotic effect. It inhibits bacterial protein synthesis through binding to ribosomal RNA, blocking the creation of the initial complex during mRNA translation, which can reduce the length of the emerging peptide chains. Analysis of the high resolution of

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the ribosomal complex has shown that LIN binds a deep cleft to the 50S subunit, which is surrounded by the complementary 23S subunit. Mutations of the 23S rRNA was demonstrated to be a LIN-resistant mechanism. LIN has been approved for the treatment of infections caused by Vancomycin-resistant *Enterococcus faecium* and hospital-acquired pneumonia caused by Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and *Streptococcus pyogenes*, which are considered the most common Gram-positive bacteria found in Intensive Care Units (ICU) [3].

In fact, LIN has gained recent interest due its use in the treatment of hospital-acquired pneumonia in Chinese tertiary-level hospitals [4]. In a retrospective analysis of the medical and reimbursement data of European adult patients who were treated for MRSA pneumonia with Linezolid or Vancomycin, it was shown that all-cause in-hospital mortality was significantly lower with LIN (23.2%) compared to 41.2% of patients who received Vancomycin. Analysis of the total cost of the ICU stay did not reveal any major differences between both treatments [5]. Moreover, in a pharmacoeconomic evaluation of antibiotics for the treatment of patients in the U.S. with complicated soft structure infection and hospital-acquired or mechanical ventilator-associated pneumonia, it was depicted that LIN was superior in terms of clinical efficacy, safety, and cost/effectiveness than Vancomycin [6]. Recently, in a murine model of MRSA pneumonia co-infected with the influenza virus, investigators demonstrated that LIN therapy improved animal survival compared to the Vancomycin group. This advantageous effect was associated with a significant attenuation of the proinflammatory cytokine response [7].

Thus, due to the aforementioned evidence, it appears time-convenient to share information concerning the pharmacokinetics of Linezolid in Mexicans (Latin population) through a well-controlled bioequivalence trial of a generic product of LIN, an antibiotic that is being included in the standardized procedures for the care of COVID-19-infected patients at intermediate-care units and ICU in tertiary-level Mexican hospitals, which could aid in providing better therapeutic management.

### What is known about this subject?

- Linezolid, a synthetic antibiotic approved for the treatment of Gram-positive bacterial infection in Intensive Care Units is being used in the treatment of hospital-acquired pneumonia preferably over Vancomycin.
- Recently, it is being used during the prophylaxis and treatment of bacterial infections associated with SARS-COV2 in tertiary-level Mexican hospitals.

### What this study adds

- Pharmacokinetic data obtained in a Mexican (Latin) population during a bioequivalence trial shows that this population is a high absorber/fast metabolizer and that the dosing-period should be adjusted in order to reach and maintain a therapeutically effective steady-state concentration.
- The Linezolid generic product was well tolerated and met the requirements of the Mexican Regulatory Agency (COFEPRIS) to be declared bioequivalent.

## MATERIALS AND METHODS

### Selection of subjects

Volunteers were recruited at the Clinical Research Unit of Pharmometrica in Mexico City. Subjects underwent screening evaluations to establish eligibility within 30 days prior to dosing of the first experimental period. Inclusion conditions were established as follows: showing willingness to participate; indistinct gender; aged between 18 and 50 years; body mass index between 18 and 27 $kg/m^2$ (inclusive); normal electrocardiogram and clinical history, and laboratory values (serum biochemistry, hematology, liver function, and urinalysis) within normal ranges, and non-smokers and without active alcoholism, negative for AIDS, hepatitis B and C, and pregnancy test for women.

Exclusion criteria comprise reports of allergy to LIN, pregnancy, positive results for the rapid assay of tetrahydrocannabinol, benzodiazepines, cocaine and methamphetamines, and any serious health condition that would affect the development of the trial. In addition, subjects who had participated in a bioequivalence study, who had donated blood, or who had been tattooed within 90 days prior to the present study were excluded. Moreover, subjects who had taken any prescription and over-the-counter medications, who had consumed xanthine-containing products, who had eaten char-broiled meals, or who had increased tobacco consumption or alcohol 48 h prior to dose administrations were also withdrawn from the study.

Volunteer withdrawal situations throughout the study considered any type of hypersensitivity reactions, the loss of two or more blood samples around $C_{max}$, vomiting between administration times and 2-fold $T_{max}$, or any dietary transgression.

### Study design

The current protocol was reviewed and authorized by the Institutional Ethics and Clinical Research Committees registered in the Mexican Regulatory Agency (COFEPRIS registration trial No. 173300410B0491/2017) and conducted in full compliance with the latest Declaration of Helsinki and in agreement with Good Clinical Practice (ICH) and Mexican regulatory guidelines for bioequivalence trials [8].

The clinical study was controlled, double-blinded (to the medical staff and the analytical investigator), cross-over, two periods (sampling up to 24 h post-dose, with a washout period of 6 days), two treatments (Zyvoxam™ 600-mg oral tablet from Pfizer, S.A. -Mexico- as Reference product and Linezolid 600-mg oral tablet produced by Laboratorios Normon, S.A. -Spain- as Test product), with two randomized administration sequences, both under fasting conditions. Experimental groups had the same number of subjects randomly assigned to each treatment sequence through a free software program [9].

The 26 selected volunteers provided their signed informed consent forms before initial screening procedures and were medically monitored along the entire trial. All subjects were confined within the clinical facility of Pharmometrica on the afternoon prior to drug administration and were assigned a number to maintain the confidentiality of their identity. They received dinner at 8 pm and fasted overnight for 12 h. An intravein catheter was placed in the non-dominant arm the following morning and pre-dose samples

were taken. At 8 am, all volunteers received a single oral dose of 600 mg of LIN of the corresponding product -according to the randomization schedule- with 250 mL of tap water. A mouth-check was done immediately after the tablets were swallowed in order to verify complete tablet intake.

Approximately 5 mL of blood was drawn from each participant for each sampling time through the catheter at 0 h (before dosing), and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 9.00, 12.00, and 24.00 h after LIN administration. Samples were collected in vacuum heparinized tubes and centrifuged at 4,000 rpm for 5 min at 20°C for plasma separation. Plasma was placed into identified cryovials and stored at -70°C until LIN quantitation [10-12]. Breakfast, lunch, and dinner were served at 10 am, 3 pm, and 9 pm, respectively.

### Bioanalytical method

After a vast review of published methods, it was decided to develop a new method based on UPLC-MS/MS and to validate this according to Mexican guidelines, US-FDA guidelines, and International considerations for the quantitation of small molecules in biological matrixes [13-15].

Briefly, 50 µL of human plasma (samples of volunteers and calibration standards) was pipetted into 1.5-mL polypropylene micro-tubes. Samples were fortified with 10 µL of Pantoprazole solution (Internal Standard). Tubes were briefly vortex-mixed, and then plasma proteins were precipitated with 200 µL of pure cold acetonitrile. Samples were vortex-mixed for 30 s and centrifuged at 17,000 × g at 4°C for 5 min. Fifty µL of supernatant was diluted with 500 µL of pure water, and 1 µL was injected into the chromatographic system (Acquity™ Class- I; Waters Co., Milford, MA, USA). A UPLC BEH C18 column (2.1 x 50 mm, 1.7-µm particle size) at 40°C was used under isocratic conditions (aqueous formic acid 0.1%: acetonitrile (77:23 v/v)) at a flux of 0.4 mL/min.

Detection was performed by positive electrospray in a tandem mass spectrometer (Xevo TQ-S Waters Micromass; Manchester, UK), employing the transitions $m/z^{1+}$ 338.43 – 296.16, and 384.27 – 200.06 for Linezolid and Pantoprazole, respectively. Linearity was demonstrated within the range of 0.1-20 µg/mL. Stability assays covered all of the quantitation-related procedures.

## STATISTICAL ANALYSIS

All statistical calculations for Pharmacokinetics (PK) were performed using Phoenix™ WinNonlin ver. 6.4 software (Pharsight Co., CA, USA). PK parameters were calculated according to the Mexican Norm NOM-177 Statistical Appendix [8] by programming plasma data, a single extravascular dose, and a non-compartmental model.

Maximal plasma drug concentration ($C_{max}$), time to reach maximal plasma concentration following drug administration ($T_{max}$), elimination half-life ($t_{½}$), area under the plasma concentration–time curve from time zero to last measurable concentration ($AUC_{0-24h}$), and AUC from time zero extrapolated to infinity ($AUC_{0-inf}$) comprised the software outputs. Linear regression of the standardized residuals and the Grubbs test (alpha 0.02) were utilized to detect atypical behaviours in the samples of the subjects evaluated.

ANOVA was employed to evaluate and discard the effects of the sequence, period, and/or treatment in the experimental design. A 90% Confidence Intervals (90% CI) of logarithm-transformed relationships for $C_{max}$, $AUC_{0-24h}$, and $AUC_{0-inf}$ between both formulations were built. Bioequivalence was concluded if the 90% CI fell within the range of 80-125% for these three PK parameters.

## RESULTS

### Demographic description

A total of 26 volunteers were enrolled in the study (13 males and 13 females); all of them completed both periods of the trial and their data were included in the pharmacokinetic and statistical analyses. Demographic data of participants were (mean ± SD): age 27.81 ± 8.06 years; height 1.63 ± 0.08 m; weight 61.75 ± 8.76 kg, and BMI 23.05 ± 2.10 $kg/m^2$.

### Safety evaluation

The duration of the clinical phase of the protocol was 11 days, including the wash-out period and the date of the last follow-up. Both reference and test products were well tolerated. Seven non-serious adverse events were reported (two dizziness, two moderate headache, one pharyngodynia, one fine tremor, and one rhinorrhea), all of these resolved during the course of the study.

### Pharmacokinetic data

Figure 1 depicts the chromatograms of Linezolid plasma concentrations; the bio-analytical method fulfilled all regulatory requirements during its validation, demonstrating linearity with accuracy and precision in a total run time of 2 min (chromatographic capacity factor [k'] = 2.32 for LIN and 4.32 for Pantoprazole). No missed samples were reported by the clinical staff, and the PK parameters for both test and reference formulations are summarized in Table 1. Mean LIN plasma concentration–time profile and a zoom for the first 4-h post-dose are shown in Figure 2.

### Statistical evaluation

Two subjects were detected as potential outliers according to the Grubbs test (*alpha* = 0.02); however, it was decided to include both volunteers in the statistical evaluation due to that there was no evidence of clinical or analytical deviations for these subjects during the development of the trial. During ANOVA, no significant sequence, period, or treatment effects were detected for log-transformed PK parameters. Neither was pre-dose concentrations detected, concluding that the clinical phase was properly conduced.

The 90% CI are reported in Table 2, showing that both formulations meet the requirements established in the Mexican regulatory guidelines for being declared bioequivalent.

## DISCUSSION

In addition to good clinical practices, a robust bio-analytical method confers reliability on the PK data. It was decided to develop and validate a method for the specific quantitation of LIN in human plasma for a bioequivalence trial. Many of the previously reported methods were focused on the quantitation of LIN, among several other antibiotics, during therapeutic drug monitoring, employing gradient elution in very long run time, or utilizing solid-phase extraction for cleaning urine, cerebrospinal fluid, or bronchial aspirations. Thus, the present method was fit-for-the purpose of

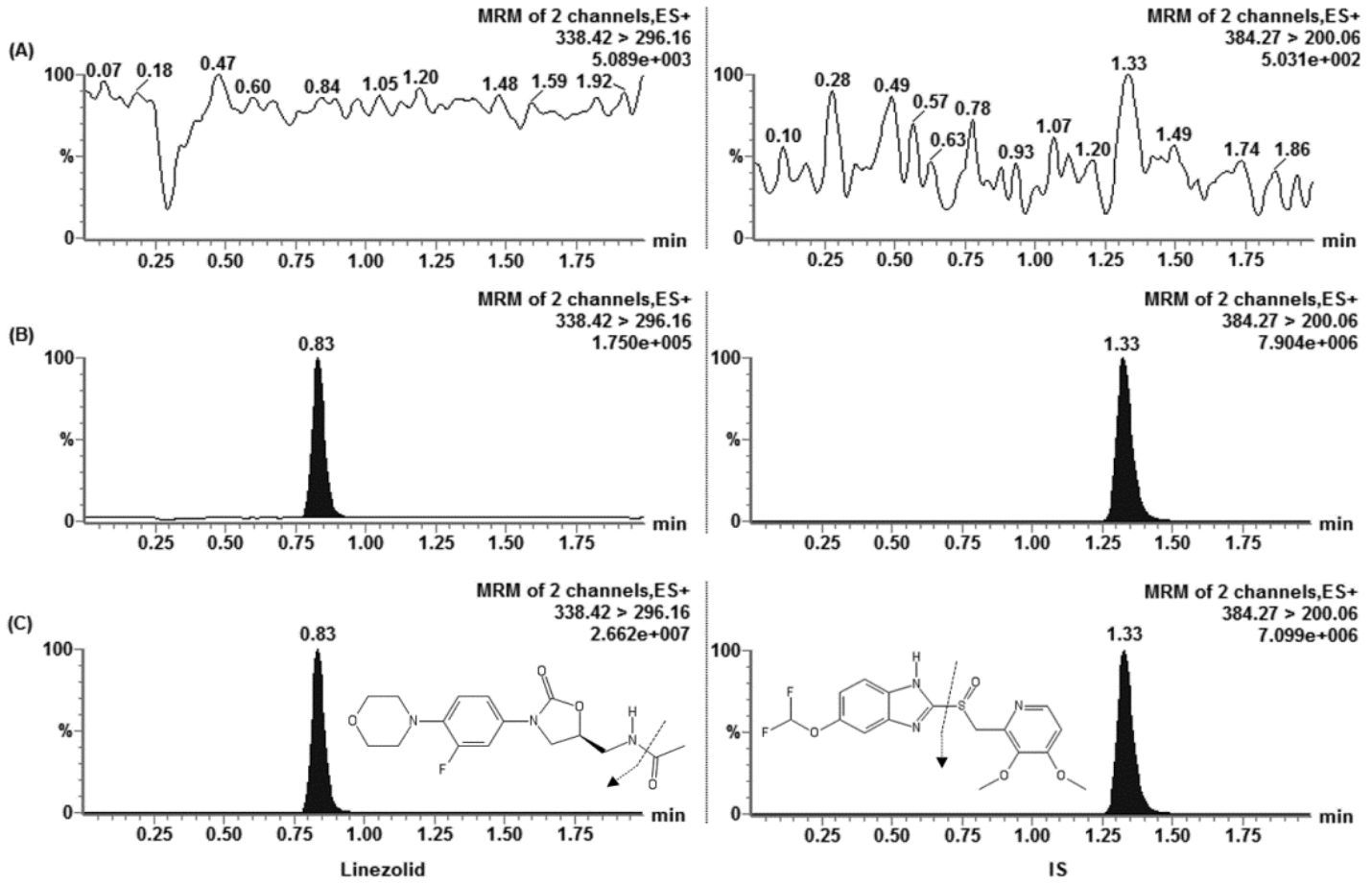


**Figure 1:** Chromatograms from individual channels of Linezolid (LIN) and internal standard Pantoprazole (PAN). A) Processed blank plasma, B) Lower Limit of Quantification (LLOQ = 0.1 µg/mL), and C) Sample of a volunteer exhibiting maximal Linezolid plasma concentration and possible fragmentation pattern during analysis.

**Table 1:** Pharmacokinetic parameters of Linezolid (LIN) after a single oral dose of one 600-mg tablet in a healthy Mexican population under fasting conditions.

| Pharmacokinetics | Zyvoxam™ | | | Linezolid test | | |
|---|---|---|---|---|---|---|
| | Min | Max | Mean | Min | Max | Mean |
| $C_{max}$ (µg/mL) | 8.89 | 29.96 | 15.33 (33.54) | 10.11 | 30.34 | 15.84 (27.94) |
| $T_{max\ (h)}$ | 0.25 | 2.5 | 0.70 (81.62) | 0.25 | 3. 00 | 0.74 (80.12) |
| $AUC_0$–24 h (µg×h/mL) | 38.81 | 115.56 | 69.75 (31.67) | 41.56 | 124.76 | 72.49 (27.78) |
| AUC0–inf (µg×h/mL) | 41.61 | 125.12 | 73.27 (30.68) | 42.74 | 130.33 | 75.27 (27.77) |
| t1/2 (h) | 2.08 | 6.66 | 3.14 (34.67) | 1.86 | 5.93 | 3.16 (30.48) |

Geometric Mean ± (%CV).
N = 26 (13 females and 13 males)
$C_{max}$ (Maximal drug plasma concentration), $T_{max}$ (Time to reach $C_{max}$), $AUC_{0\text{-}24h}$ (Area under the Curve up to 24 h), $AUC_{0\text{-}inf}$ (Area under the curve extrapolated to infinity), $t_{½}$ (Plasma elimination half-life).

this trial.

Concerning PK data, it is interesting to note that Mexicans are higher and slightly faster absorbers compared to other populations (Table 3). $C_{max}$ in this sample population was 18% higher than that observed in Chinese volunteers, and nearly 75% higher than that reported for Egyptians. In terms of $T_{max}$, there were no significant differences among compared populations, except, again, for Egyptians, who appear to be slow absorbers. The most remarkable differences were in terms of the total amount of absorbed LIN ($AUC_{0\text{-}inf}$) and how fast it was eliminated. Apparently, Mexican population is a faster metabolizer; their $AUC_{0\text{-}inf}$ was 60% of those reported for Egyptians and 74% of those Indian population data. However, the most evident differences were found in the $t_{½}$: while the plasma elimination half-life of Mexican subjects was 35% faster than those of Chinese and Indian populations, it was 63% faster than Egyptians. In all of these three reports, the plasma concentration of LIN appeared to entertain a plateau condition between the 3-h and the 10-h post-dose.

These data may suggest that the information for prescription provided by the Reference product would not be applicable in Mexican population regarding LIN dosing every 12 h to reach and maintain a steady state. It has been previously reported that, with an oral dose of 600 mg every 12 h in patients without renal impairment, $C_{max}$ and $C_{min}$ during steady state were 21.2 µg/mL and 6.15 µg/mL, respectively [2]. This indicates a fluctuation of approximately 345% in the original studied populations. The latter

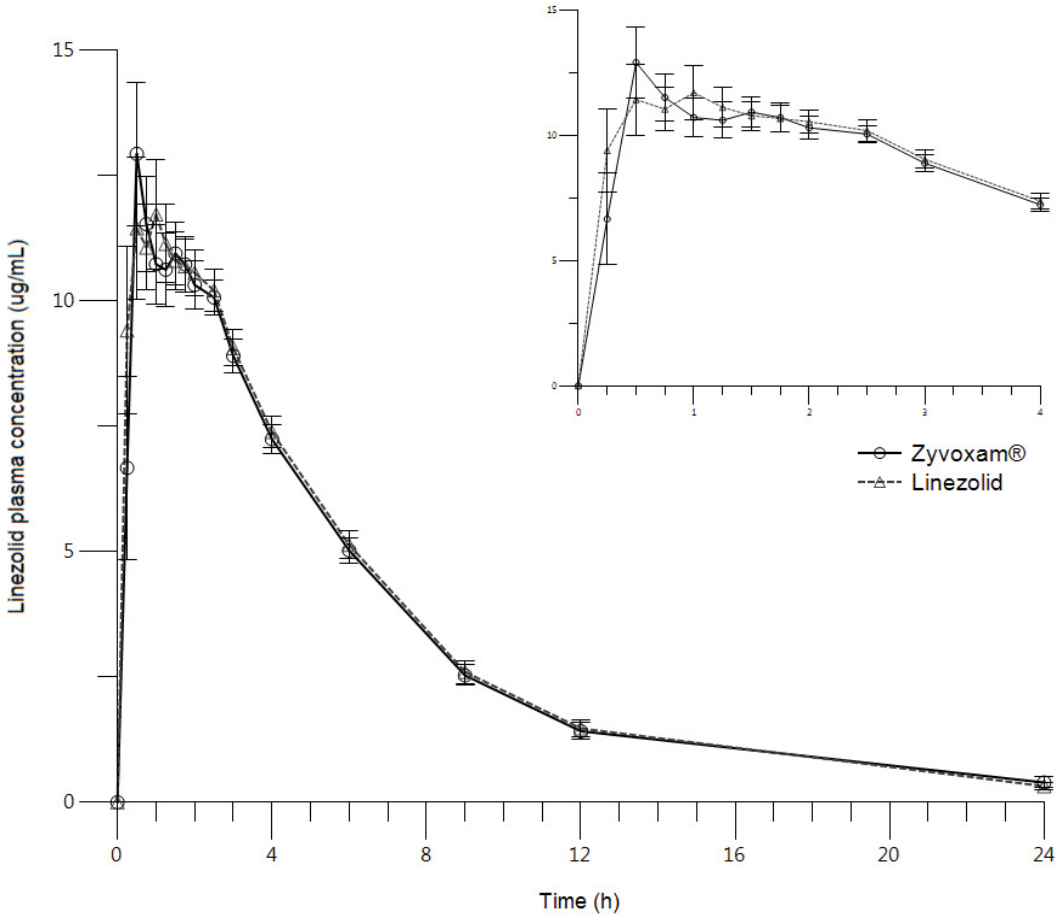


**Figure 2:** Plasma concentration–time profile of Linezolid (LIN) after a single oral dose of one 600 mg tablet of Zyvoxam™ or Linezolid test product, in a healthy Mexican population under fasting conditions, and a zoom for the first 4-h post-dose. Data are expressed as means ± Standard Error (SE).

**Table 2:** Statistics bioequivalence of Linezolid 600 mg immediate - release tablets (Test product) and Zyvomax™ 600 mg tablets.

| Parameters | Intra-subject %CV | 90% Confidence Intervals | | % Ratio (Test/Reference) |
|---|---|---|---|---|
| | | Lower | Upper | |
| log ($C_{max}$) | 24.99 | 91.94 | 116.14 | 103.33 |
| log ($AUC_{0-24h}$) | 13.81 | 97.38 | 110.95 | 103.94 |
| log ($AUC_{0-inf}$) | 13.25 | 96.50 | 109.37 | 102.74 |

**Table 3:** Pharmacokinetics of Linezolid after a single oral dose of one 600-mg tablet in different populations during bioequivalence trials (Mean ± Standard Deviation).

| Pharmacokinetics | Indian[10] population | Egyptian[11] population | Chinese[12] population |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 12.88 ± 2.48 | 9.20 ± 1.90 | 13.70 ± 3.50 |
| $T_{max}$ (h) | 1.02 ± 0.73 | 2.90 ± 1.40 | 1.50 ± 1.20 |
| $AUC_{0-inf}$ (µg*h/mL) | 103.50 ± 29.23 | 128.40 ± 32.10 | 112.60 ± 24.90 |
| $t_{1/2}$ (h) | 5.07 ± 1.61 | 8.90 ± 1.10 | 5.13 ± 0.92 |
| Sample size (N) | 12 males | 28 males | 20 males |

$C_{max}$ (Maximal drug plasma concentration), $T_{max}$ (Time to reach $C_{max}$), $AUC_{0-inf}$ (Area under the curve extrapolated to infinity), $t_{½}$ (Plasma elimination half-life).

must be more widespread in faster metabolizers and might represent longer periods of time under the therapeutic concentrations of LIN with the possible presentation of concomitant bacterial resistance.

Therefore, knowing that the dosing time can be calculated by multiplying the target concentration for total clearance (clearance = dose/$AUC_{0-inf}$) [16] and considering a target plasma concentration of 13.675 µg/mL (geometric mean between the $C_{max}$ and $C_{min}$ during steady state), the LIN 600 mg-tablet should be administered at least every 6 h in order to achieve and maintain a therapeutically useful steady state.

## CONCLUSION

The test formulation (Linezolid 600-mg tablets) met the COFEPRIS criteria of bioequivalence as compared with Zyvoxam™ of Pfizer S.A. México after a single oral dose under fasting conditions, exhibiting similar adverse effects to those of the reference product.

The contribution of this type of clinical trials lies in their evidencing differences in pharmacokinetics among populations and the need to customize pharmacological treatments, based on the evidence of individual therapeutic drug monitoring.

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## FINANCIAL DISCLOSURE

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

## ETHICAL CONDUCT OF RESEARCH

The authors state that the clinical protocol was reviewed and approved by an independent Ethics Committee. In addition, the authors obtained COFEPRIS approval for the conduction of present study. Volunteers signed informed consent, which was formulated according to the latest version of the Declaration of Helsinki (64th General Meeting, Fortaleza, Brazil, October 2013).

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