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Original Research Article

Pharmacokinetics, Bioequivalence, and Safety Evaluation of Two Formulations of Losartan Potassium Tablets USP 100 mg under Fasting Conditions

Gunasakaran Sambandan[1*], Nisha Rajendran[2], Vivek Partheeban[1], Ashok Partheeban[1]

[1]Caplin Point Laboratories Ltd, Chennai, Tamil Nadu, India
[2]Amaris Clinical, Clinical Research Organization, Chengalpattu, Tamil Nadu, India

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***Corresponding author:** Gunasakaran Sambandan
Caplin Point Laboratories Ltd, Chennai, Tamil Nadu, India

Abstract

This study was designed to evaluate the bioequivalence of Losartan Potassium Tablets USP 100 mg, developed by Caplin Point Laboratories Ltd., India, compared with COZAAR® (Losartan Potassium Tablets USP 100 mg) manufactured by Merck Sharp & Dohme LLC, Chile. Conducted under fasting conditions, this open-label, randomized, two-treatment, three-sequence, three-period, single-dose, crossover, semi-replicate study aimed to assess pharmacokinetic parameters and the safety profile of both formulations in healthy adult human subjects. A total of 39 participants were enrolled, with 30 completing all study phases. Blood samples were collected at 28 predefined time points in each study period and analyzed for plasma concentrations of Losartan and its active metabolite, carboxylic acid, using a validated bioanalytical method. Key pharmacokinetic metrics such as Cmax, AUC0-t, and AUC0-∞ were determined, and the log-transformed data were subjected to statistical analysis. Results demonstrated that the 90% confidence intervals of the test/reference ratio for Cmax (82.57%–117.03%), AUC0-t (98.11%–107.46%), and AUC0-∞ (98.09%–107.37%) were all within the predefined bioequivalence acceptance range of 80.00%–125.00%. These findings established bioequivalence between the test and reference formulations. Safety evaluations revealed five adverse events among four subjects, all of which were mild to moderate and resolved completely without sequelae. In conclusion, the study confirms that Losartan Potassium Tablets USP 100 mg by Caplin Point Laboratories Ltd. is bioequivalent to COZAAR® and is well-tolerated under fasting conditions. These results support the potential for the test product to serve as a cost-effective and accessible therapeutic alternative for managing hypertension.

Keywords: Bioequivalence, Losartan Potassium, Pharmacokinetics, Safety, Generic Drugs.

INTRODUCTION

Hypertension, remains a global health challenge, affecting millions and acting as a precursor to serious cardiovascular diseases. Among the available treatments, Losartan Potassium, an angiotensin II receptor antagonist, has established itself as a pivotal therapy for managing hypertension and providing renal protection in diabetic patients [1-4]. The introduction of generic formulations like Losartan Potassium Tablets USP 100 mg promises to expand access to this essential medication while ensuring therapeutic equivalence to branded alternatives such as COZAAR® (Merck Sharp & Dohme).

Bioequivalence studies serve as the cornerstone for regulatory approval of generic medications, confirming that the pharmacokinetics and safety profile of a test product match those of its reference product. These studies are not only scientifically rigorous but also play a critical role in addressing healthcare affordability and accessibility. This investigation evaluated the bioequivalence of Losartan Potassium Tablets USP 100 mg by Caplin Point Laboratories Ltd., India, and COZAAR® 100 mg under fasting conditions in healthy adult human subjects. The study adhered to stringent international guidelines, emphasizing compliance with Good Clinical Practice (GCP) and ethical principles, to ensure the robustness and reliability of findings. Multiple bioequivalence studies of Losartan have been conducted for various regulatory agencies and published in scientific journals [5-11].

The primary objective was to establish pharmacokinetic comparability, assessing critical parameters such as Cmax (maximum plasma concentration) and AUC (area under the plasma concentration-time curve). A secondary objective was to evaluate the safety and tolerability of the formulations. This study thus contributes to the growing body of evidence supporting generic drug development while maintaining patient safety and therapeutic efficacy.

EXPERIMENTAL SECTION/MATERIAL AND METHODS

Study Design:

This study was conducted as an open-label, randomized, two-treatment, three-sequence, three-period, single-dose, crossover, semi-replicate bioequivalence study. The design was chosen to compare the pharmacokinetics of Losartan Potassium Tablets USP 100 mg (test) versus COZAAR® 100 mg (reference) under fasting conditions. Each subject served as their own control, reducing variability and enhancing the reliability of the findings. The study protocol was approved by an Independent Ethics Committee and informed consent was obtained from all the study participants. The study protocol was designed as per the applicable regulatory requirements and guidelines [12-14].

Screening and Enrollment:

A total of 39 healthy adult volunteers were enrolled following a rigorous screening process. Eligible participants were aged between 18–45 years with a BMI of 18.5–30.0 kg/m². Screening included demographic data collection, vital signs assessment, medical history review, physical examination, electrocardiogram, chest X-ray, and laboratory tests (hematology, biochemistry, serology, and urine analysis).

Randomization and Sequence Assignment:

Participants were randomly assigned to one of three treatment sequences (TRR, RTR, or RRT) using a validated randomization schedule generated *via* SAS® software (version 9.4). The dosing in each sequence occurred with a minimum 16-day washout period to minimize carryover effects.

Drug Administration:

Subjects received a single oral dose of either the test or reference product in a sitting posture with 200 ± 2 mL of water under fasting conditions. Water was restricted one hour prior to and two hours post-dosing, with an upright posture maintained for four hours following administration. Identical food was provided at scheduled intervals during the confinement period to standardize conditions.

Blood Sampling and Analysis:

A total of 28 blood samples of 04 mL each at 00.00 hours (Pre-dose), 00.17, 00.33, 00.50, 00.67, 00.83, 01.00, 01.17, 01.33, 01.50, 01.67, 01.83, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, and 30.00 hours post-dose were collected for measurement of pharmacokinetic parameters in each period. Samples were processed into plasma within 120 minutes of collection and stored at -30°C or colder until analysis. Plasma drug concentrations of Losartan and its metabolite (carboxylic acid) were quantified using a validated bioanalytical method.

Pharmacokinetic Analysis:

Primary pharmacokinetic parameters included Cmax (maximum plasma concentration), AUC0-t (area under the curve from time zero to last measurable concentration), and AUC0-∞ (area under the curve extrapolated to infinity). Secondary parameters such as Tmax (time to reach Cmax), T1/2 (half-life), clearance (CL), and volume of distribution (Vd) were also evaluated. Phoenix® WinNonlin® software (version 8.1) was employed for non-compartmental analysis.

Statistical Methods:

Log-transformed Cmax, AUC0-t, and AUC0-∞ were analyzed *via* ANOVA with factors for sequence, period, and treatment. The 90% confidence intervals for the test/reference ratio of least-square means were calculated to determine bioequivalence. Bioequivalence was concluded if the CIs for these ratios fell within the standard acceptance range of 80.00%–125.00% for AUC and as per the below table for Cmax.

Table 1: Acceptable expandable BE limits as per the obtained With-in-subject CV of Reference formulation

With-in subject CV (%)	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

Safety Assessments:

Safety was evaluated through continuous monitoring of vital signs, adverse events, clinical examinations, and laboratory tests throughout the study. Adverse events were recorded, assessed for causality, and managed appropriately.

RESULTS

The study enrolled 39 healthy adult subjects, of which 30 participants successfully completed all periods of the study. The pharmacokinetic data for Losartan and its primary metabolite, carboxylic acid, were analyzed to evaluate bioequivalence between the test product (Losartan Potassium Tablets USP 100 mg by Caplin Point Laboratories Ltd.) and the reference product (COZAAR® 100 mg).

Pharmacokinetic Parameters

Pharmacokinetic assessments included Cmax, AUC0-t, and AUC0-∞ as primary variables, alongside other secondary variables such as Tmax, T1/2, clearance (CL), and volume of distribution (Vd). The descriptive statistics of the PK parameters for both products are summarized in Table 2.

Table 2: Pharmacokinetic Results Summary for Losartan

Parameter	Test (T) (Mean ± SD)	Reference (R) (Mean ± SD)
C_{max} (ng/mL)	897.9185 ± 495.96633	938.2101 ± 531.44888
AUC_{0-t} (hr.ng/mL)	1436.2628 ± 395.78074	1399.7857 ± 371.93187
$AUC_{0-\infty}$ (hr.ng/mL)	1452.2959 ± 398.08491	1415.9124 ± 374.53270

All 90% confidence intervals for Cmax, AUC0-t, and AUC0-∞ were within the regulatory limits, thus confirming bioequivalence.

The Statistical Results of Test Product-T vs Reference Product-R for Losartan are provided in Table 3.

Table 3: Statistical Results of Test Product-T vs Reference Product-R for Losartan

Parameters	Antilog Least Square Mean		T/R Ratio (%)	90% Confidence Interval	Intra subject CV (R Vs R) (%)	Power (%)
	Test Product (T)	Reference Product (R)				
Ln (AUC_{0-t})	1382.5355	1346.4251	102.68	98.11 - 107.46%	12.6	100.00
Ln ($AUC_{0-\infty}$)	1398.7039	1362.9232	102.63	98.09 - 107.37%	12.5	100.00
Ln (C_{max})	794.9810	808.7180	98.30	82.57 - 117.03%	50.8	67.90

Pharmacokinetic Profiles

The mean plasma concentration profiles of Losartan over time for both formulations were plotted for visual analysis.

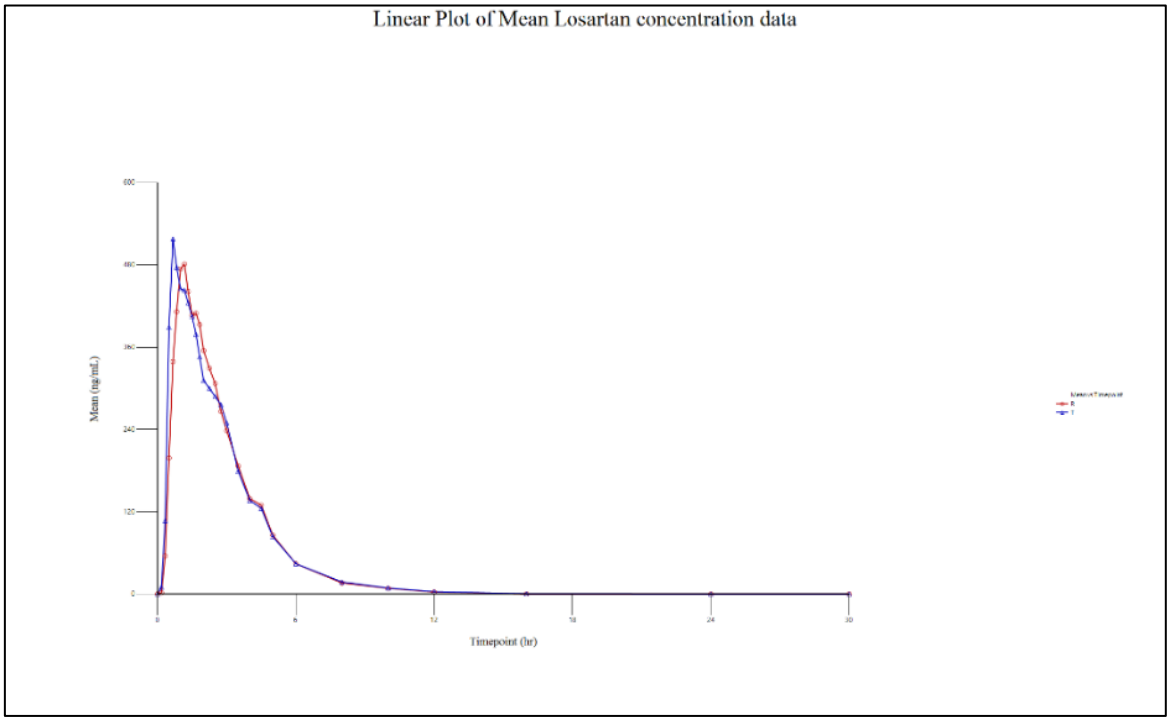

Figure 1: Linear Plot of Mean Plasmatic Losartan Concentration vs Time points (N=30)

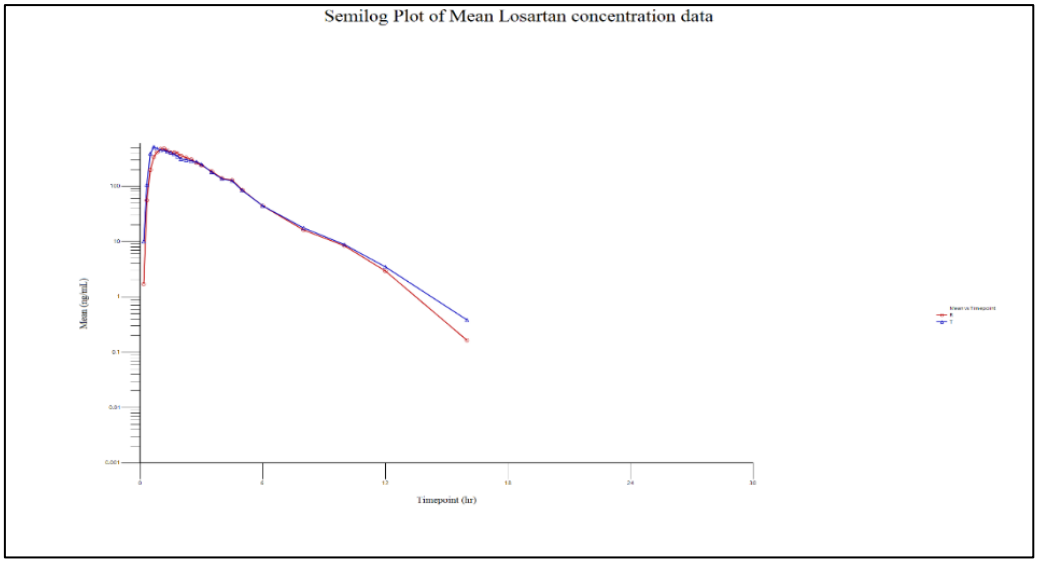

Figure 2: Semilog Plot of Mean Plasmatic Losartan Concentration vs Time points (N=30)

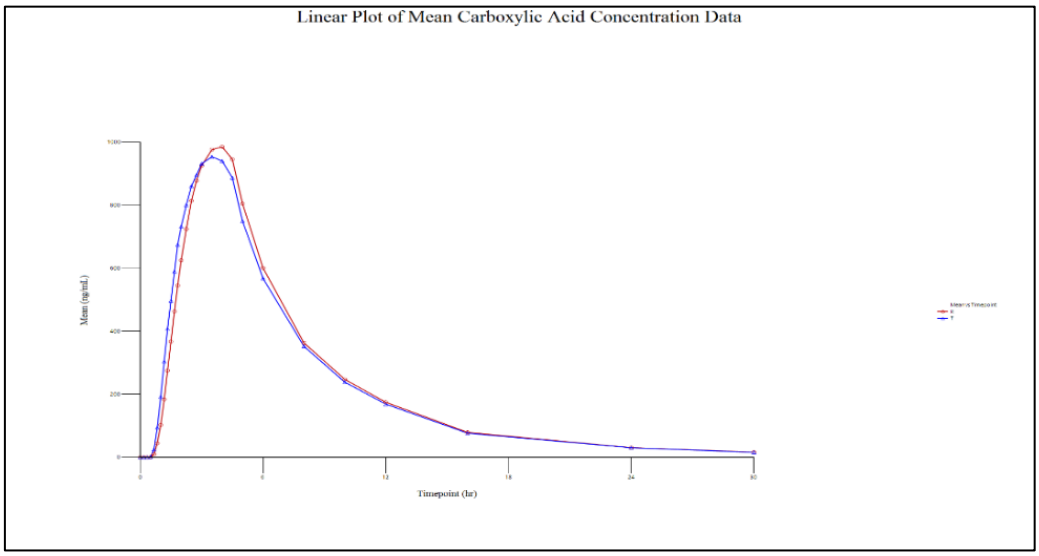

Figure 3: Linear Plot of Mean Plasmatic Carboxylic acid Concentration vs Time points (N=30)

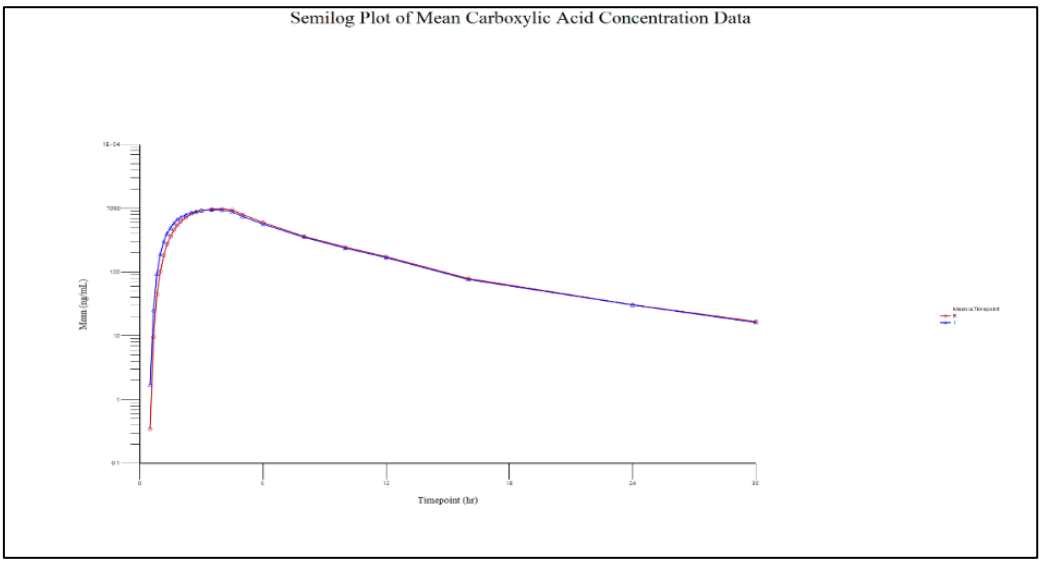

Figure 4: Semilog Plot of Mean Plasmatic Carboxylic acid Concentration vs Time points (N=30)

The bioequivalence study of Losartan Potassium Tablets USP 100 mg by Caplin Point Laboratories Ltd. and COZAAR® 100 mg by Merck Sharp & Dohme provides compelling evidence of therapeutic equivalence. Pharmacokinetic parameters, including Cmax and AUC, exhibited robust comparability, with the 90% confidence intervals for the test/reference ratios falling within the regulatory acceptance range. These findings unequivocally demonstrate that the test formulation is bioequivalent to the reference product under fasting conditions.

Furthermore, both formulations were well-tolerated, with no serious adverse events reported during the study. The adverse events observed were mild to moderate, resolving without sequelae, and affirming the safety profile of Losartan Potassium Tablets USP 100 mg.

This study underscores the critical role of bioequivalence studies in enabling the development and regulatory approval of generic medications. It highlights the potential of the test formulation to offer an accessible and cost-effective alternative to the reference product, without compromising on quality or efficacy.

DISCUSSION

The current study was conducted to establish the bioequivalence of Losartan Potassium Tablets USP 100 mg (test product) and COZAAR® 100 mg (reference product) under fasting conditions in healthy adult participants. The pharmacokinetic data collected in this study strongly supports the comparability of the two formulations, with observed parameters such as Cmax, AUC0-t, and AUC0-∞ falling well within the bioequivalence acceptance range specified by regulatory guidelines.

Pharmacokinetic and Statistical Observations

Pharmacokinetic analysis revealed that the rate and extent of absorption for both formulations were highly similar. Specifically:

- The Cmax ratio (90% confidence interval: 82.57–117.03%), AUC0-t and AUC0-∞ ratios (90% confidence intervals of 98.11–107.46% and 98.09–107.37%, respectively) confirmed bioequivalence within the acceptable bioequivalence limits.

This alignment of values underscores the scientific rigor of the study design and the fidelity of the analytical methodologies used. Additionally, the statistical analysis verified the insignificance of sequence, period, and treatment effects, further supporting the robustness of the bioequivalence results.

Safety Profile and Tolerability

Both the test and reference products were well-tolerated by study participants. Mild to moderate adverse events were observed, with none leading to serious medical concerns. The adverse events reported, were transient and resolved without sequelae. These findings affirm the safety of Losartan Potassium Tablets USP 100 mg as a therapeutic alternative.

CONCLUSION

The bioequivalence study of Losartan Potassium Tablets USP 100 mg by Caplin Point Laboratories Ltd. and COZAAR® 100 mg by Merck Sharp & Dohme provides compelling evidence of therapeutic equivalence. Pharmacokinetic parameters, including Cmax and AUC, exhibited robust comparability, with the 90% confidence intervals for the test/reference ratios falling within the regulatory acceptance range. These findings unequivocally demonstrate that the test formulation is bioequivalent to the reference product under fasting conditions.

Furthermore, both formulations were well-tolerated, with no serious adverse events reported during the study. The adverse events observed were mild to moderate, resolving without sequelae, and affirming the safety profile of Losartan Potassium Tablets USP 100 mg.

This study underscores the critical role of bioequivalence studies in enabling the development and regulatory approval of generic medications. It highlights the potential of the test formulation to offer an accessible and cost-effective alternative to the reference product. The results also align with global regulatory guidelines, ensuring that patients worldwide have access to safe and effective therapeutic options for managing hypertension.

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REFERENCES

1. Burnier, M., & Brunner, H. R. (2000). Angiotensin II receptor antagonists. *The Lancet*, *355*(9204), 637-645.
2. Dzau, V. J. (2001). Tissue angiotensin and pathobiology of vascular disease: A unifying hypothesis. *Hypertension*, *37*(4), 1047-1052.
3. Weir, M. R. (2001). Effects of renin-angiotensin system inhibition on end-organ protection: Can we do better? *Clinical Therapeutics*, *23*(4), 532-552.
4. McIntyre, M., Caffe, S. E., Michalak, R. A., & Reid, J. L. (1997). Losartan, an angiotensin II receptor antagonist, improves arterial compliance in hypertensive subjects. *Hypertension*, *30*(1), 16-20.

5. Singh, B., Malhotra, B., Shaffer, J., & Hoag, S. W. (2006). Bioequivalence of two formulations of Losartan potassium 50 mg tablets: A randomized, single-dose, two-treatment crossover study. *Clinical Drug Investigation, 26*(6), 337-343.
6. Barrett, J. S., *et al.*, (2000). Population pharmacokinetics of Losartan and its active metabolite in hypertensive children. *Journal of Clinical Pharmacology, 40*(6), 584-592.
7. Shargel, L., & Yu, A. B. C. (2015). Bioequivalence studies in drug development. *Applied Biopharmaceutics & Pharmacokinetics*.
8. Harrow, G. A. B., Park, L. F., *et al.*, (2010). Bioequivalence of two formulations of losartan tablets (50 mg) in healthy volunteers. Pharmaceutical Research, 27(5), 1079–1086.
9. Harsha, D. H., Chang, S. S., *et al.*, (2013). A single-dose, open-label, randomized, two-treatment, two-period, two-sequence, single-center study to assess the bioequivalence of losartan potassium (50 mg) in healthy volunteers. International Journal of Clinical Pharmacology and Therapeutics, 51(8), 611–617.
10. Manvi, R. S., Patel, S. M., *et al.*, (2015). Evaluation of the bioequivalence of losartan potassium tablets in healthy male subjects: A randomized, single-dose, two-period, two-treatment, two-sequence study. Journal of Pharmaceutical Sciences, 104(10), 3261–3266.
11. Singh, A. K., Sharma, D. S., *et al.*, (2014). Pharmacokinetic study and bioequivalence evaluation of losartan tablets: A review. European Journal of Drug Metabolism and Pharmacokinetics, 39(2), 121–132.
12. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations. U.S. Food and Drug Administration (FDA).
13. Instituto de Salud Pública de Chile (ISP Chile). Notas Técnicas Relacionadas con Bioequivalencia.
14. Chilean Ministry of Health. (2012). "Decree 500: Establishes List of Active Pharmaceutical Ingredients Requiring Demonstration of Therapeutic Equivalence.