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Research Article

# Randomized, Open-Label, Two-Way Crossover Study to Compare the Bioequivalence of PRELIN™ and LYRICA™ Among Bangladeshi Male Volunteers

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## ABSTRACT

**Background:** Pregabalin, an anticonvulsant and neuropathic pain agent, acts by binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, reducing neurotransmitter release. It is commonly prescribed for epilepsy, generalized anxiety disorder, and fibromyalgia. Assessing bioequivalence between generic and branded formulations is critical to ensure consistent therapeutic effects.

**Objective:** This study aimed to compare the bioequivalence of two 150 mg oral pregabalin capsules PRELIN™ (Drug International Ltd., Bangladesh) as the test product and LYRICA™ (Pfizer Laboratories) as the reference in healthy Bangladeshi male subjects.

**Methods:** A randomized, two-period, two-sequence crossover study was conducted in 16 healthy male volunteers. Each participant received a single 150 mg dose of either formulation after fasting, with a washout period of over one week between treatments. Plasma pregabalin levels were measured over 24 hours using validated LC-MS/MS. Key pharmacokinetic parameters ($C_{max}$, $T_{max}$, $AUC_{0-24h}$, $t_{½}$, and $K_{el}$) were calculated using non-compartmental analysis.

**Results:** The mean $AUC_{0-24h}$ was 105.0 ± 32.8 ng·h/mL for PRELIN™ and 126.9 ± 40.0 ng·h/mL for LYRICA™, indicating a relative bioavailability of 82.7%. $C_{max}$ values were 36.2 ± 10.4 ng/mL (PRELIN™) and 40.3 ± 9.4 ng/mL (LYRICA™), while $T_{max}$was 1.4 ± 0.7 hours and 1.1 ± 0.3 hours, respectively. Elimination half-life was 4.6 ± 1.6 hours for PRELIN™ and 4.1 ± 3.6 hours for LYRICA™, with corresponding $K_{el}$ values of 0.1642 $h^{-1}$ and 0.0975 $h^{-1}$.

**Conclusion:** PRELIN™ exhibited pharmacokinetic parameters similar to LYRICA™, although its relative bioavailability was slightly below the standard bioequivalence threshold. Nonetheless, both formulations showed comparable absorption profiles.

**Keywords:** Bioequivalence, LC-MS, Pharmacokinetics

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## INTRODUCTION

Pregabalin is a structural analogue of γ-amino butyric acid (GABA), which is an anticonvulsant and anxiolytic agent, generally used for nerve pain, epilepsy, Generalized anxiety disorder and Fibromyalgia (widespread muscle pain) [1–4]. Pregabalin binds with high affinity to the $\alpha_2\delta$ subunit of voltage-gated calcium channels in the central nervous system which reduces calcium entry into nerve cells, results in decreasing the release of excitatory neurotransmitters like glutamate, noradrenaline, and substance P that helps relieve neuropathic pain, seizures and anxiety symptoms[5-9].

LYRICA™ (pregabalin), developed by Pfizer Inc., received its first U.S. FDA approval in 2004 and has since been widely prescribed for multiple conditions, including diabetic peripheral neuropathy, post herpetic neuralgia, adjunctive therapy for partial-onset seizures, fibromyalgia, **and** neuropathic pain associated with spinal cord injury[10].

It is available in a number of formulations and is distinguished by its high oral bioavailability (>90%), quick absorption, and unchanged renal excretion, all of which add to its predictable pharmacokinetic profile[11-13].

A major turning point was reached when the patent for pregabalin expired, allowing pharmaceutical companies all over the world to create and sell generic versions of the drug. This increased accessibility and affordability for a larger patient population, particularly in low- and middle-income nations, by encouraging market competition and significantly lowering the cost of therapy[14]. Among these, PRELIN™ is a locally manufactured generic alternative in Bangladesh by Drug International Ltd., containing 150 mg of pregabalin per capsule.

However, according to regulatory guidelines established by the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and other global agencies, for the approval of a generic formulations, it is crucial to establish bioequivalence to ensure that the efficacy and safety of the test product are comparable to those of the reference product.

Bioequivalence is the absence of a significant difference in the rate and degree to which the active ingredient or active moiety becomes available at the site of action, when given at the same molar dose under comparable conditions in a suitably planned trial. By proving this equivalency using pharmacokinetic metrics like $C_{max}$ and AUC, the generic product's physiological performance is confirmed to be comparable to that of the original formulation. The maximum plasma concentration ($C_{max}$), the area under the plasma concentration-time curve from zero to the last measurable point ($AUC_{0-t}$), and the total drug exposure over time estimated as the area under the curve from zero to infinity ($AUC_{0-\infty}$) were the main pharmacokinetic parameters evaluated to determine bioequivalence[15–17].

Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS) is a highly sensitive and specific analytical technique widely used during bioequivalence studies to measure drug concentrations in biological samples, such as plasma due to its' high selectivity, rapid analysis with high throughput and accurate and precise quantification After administering both the test (generic) and reference (brand) formulations to healthy volunteers in a controlled clinical environment, blood samples are then collected at predetermined time points. LC-MS/MS enables accurate quantification of the active drug (e.g., pregabalin) by separating it from other plasma components (via liquid chromatography) and detecting it based on its mass-to-charge ratio (via mass spectrometry)[18–21]. To find out if the test and reference formulations met the predetermined acceptance limits for bioequivalence, which are usually set at 80.00%–125.00% for the 90% confidence interval of the ratio of the log-transformed $C_{max}$ and AUC values, the pharmacokinetic parameters were computed and statistical analyses were conducted [22-24].

This study was focused on the bioequivalence of PRELIN™ (Drug International Ltd., Bangladesh) in comparison to LYRICA™ (Pfizer Laboratories) by measuring plasma concentrations of pregabalin using a validated LC-MS/MS method. The pharmacokinetic parameters were calculated, and statistical analyses were performed to determine whether the test and reference formulations fall within the predefined acceptance limits for bioequivalence.

## Objectives of the Investigation

The objective of this study was to assess the bioequivalence of the test product, PRELIN™ (pregabalin 150 mg capsule; Drug International Ltd., Bangladesh), in comparison with the reference product, LYRICA™ (pregabalin 150 mg capsule; Pfizer Laboratories), through the determination of plasma drug concentrations using a validated LC-MS/MS method and the calculation of standard pharmacokinetic and bioequivalence parameters.

## Protocol

Randomized, open-label, two-way crossover bioequivalence study with a washout period of more than 7 days. There was no major deviation made from the approved protocol.

## Materials and Methods

### Study Subjects

Participants were recruited from a volunteer database and enrolled through individual counseling. A total of sixteen healthy male volunteers participated in the study. The mean age of the subjects was 29.2 ± 4.6 years, with an average height of 167.0 ± 4.5 cm and weight of 59.6 ± 5.9 kg at the time of screening. Blood samples were collected in two distinct phases following drug administration. Phase I was conducted from September 9 to 11 and September 17 to 19, 2013, while Phase II took place from September 12 to 14 and September 20 to 22, 2013. The collected samples were analyzed between January 4 and May 10, 2014.

### Study Medications

Two formulations of Pregabalin 150 mg capsules were used in the study. Treatment A (test formulation) was PRELIN™ (Batch No. 0113), manufactured in February 2013 and set to expire in February 2015 by Drug International Ltd., Bangladesh. Treatment B (reference formulation) was LYRICA™ (Batch No. 0728120), manufactured in December 2010 with an expiry date of November 2013, produced by Pfizer Laboratories.

### Dosage Regimen

Each participant received a single dose of both the test and reference formulations in accordance with a randomized, two-period, two-sequence crossover design. A washout period of more than seven days separated the two treatment phases.

### Ethical Considerations

The study protocol and ethical aspects were reviewed and approved by the Institutional Review Board of KhwajaYunus Ali Medical College Hospital. The board consisted of seven members, including a legal advisor, a local religious leader (Imam), and a female representative. The study was approved with minor amendments and was

conducted in compliance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, as adopted by the European Medicines Agency (EMA).

## Informed Consent

Prior to enrollment, the study objectives and procedures were explained to each volunteer in Bengali by a medical officer. Written informed consent was obtained from participants who voluntarily agreed to take part in the study after thoroughly reviewing the consent form. All participant queries were addressed in detail by the medical officer, and a copy of the signed consent form was retained as part of the study protocol.

## Hospital Admission

Following successful screening, participants were admitted to a dedicated 12-bed hospital ward designed specifically for bioequivalence studies. Admission occurred one day prior to the initiation of each study phase. The ward was equipped with recreational amenities, including a 20-inch color television and a carom board, to provide entertainment during periods of rest. A maximum of eight volunteers were accommodated in the ward at any given time to ensure proper monitoring and comfort.

## Drug Administration and Sample Collection

Each participant received a single oral dose of either the test or reference formulation of Pregabalin with 250 mL of water after an overnight fast of at least nine hours. Water intake was permitted two hours post-dose, followed by breakfast at four hours, and subsequent meals (lunch and dinner) provided according to a standardized schedule. Volunteers remained under continuous medical supervision throughout the study period.

Blood samples (2 mL each) were collected pre-dose and at 0.3, 0.6, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours post-dose. Samples were collected in EDTA tubes, centrifuged at 4000 rpm for 10 minutes to separate plasma, which was then stored at –80°C in labeled Eppendorf tubes until analysis. The crossover phase was conducted after a seven-day washout period, following identical procedures.

## Drug Analysis

Plasma concentrations of pregabalin were quantified using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. The retention time of pregabalin was recorded at 2.45 minutes. The assay method demonstrated a limit of detection (LOD) of 16 ng (3 standard deviations) and a limit of quantification (LOQ) of 54 ng (10 standard deviations). Pharmacokinetic parameters were determined as follows: the extent of absorption was measured using the area under the plasma concentration–time curve from 0 to 24 hours ($AUC_{0\rightarrow 24}h$); the rate of absorption was assessed using maximum plasma concentration (Cmax) and time to reach maximum concentration ($T_{max}$); and elimination characteristics were evaluated using the half-life (t½) and elimination rate constant (Kel) of pregabalin.

## Sample Preparation for LC-MS/MS

Plasma samples for LC-MS/MS analysis of pregabalin were prepared by protein precipitation. Briefly, 200 µL of thawed plasma was mixed with 800 µL of acetonitrile containing the internal standard, vortexed for 1 minute, and centrifuged at 13,000 rpm for 10 minutes at 4°C. The supernatant was filtered through a 0.22 µm syringe filter, and a 5 µL aliquot was injected into the LC-MS/MS system. Chromatographic separation was performed using a $C_{18}$ reversed-phase column with a mobile phase of water and acetonitrile containing formic acid. Pregabalin was detected using positive electrospray ionization in MRM mode, with a retention time of approximately 2.45 minutes. The method was validated according to international bioanalytical guidelines for accuracy, precision, linearity, and stability.

## Statistical analysis

Pharmacokinetic parameters under the curve (AUC0→t, AUC0→α,), peak exposure ($C_{max}$), time-to-peak exposure ($T_{max}$), half-life ($t_{½}$) and elimination rate constant ($K_{el}$) for the two formulations (test and reference products) were calculated by two-way analysis of variance (ANOVA) procedure using ThermoKinetica updated software. The 90% confidence interval was calculated using online software.

## Pharmacokinetic analysis

The pharmacokinetic parameters $C_{max}$, $T_{max}$, $AUC_{0\rightarrow 24h}$, $t_{1/2}$, and $K_{el}$ were determined. The mean (± SD) $AUC_{0\rightarrow 24h}$ for pregabalin of test drug **PRELIN**™ for 16 volunteers was 105.0 ± 32.8 ng/hr/mL whereas it was 126.9 ± 40.0 ng/hr/mL for pregabalin of **LYRICA**™.The relative bioavailability (**PRELIN**™/**LYRICA**™ ratio) was 82.7%. The $C_{max}$, $t_{max}$, half-life of elimination ($t_{1/2}$) and the rate of elimination ($K_{el}$) of pregabalin of test drug were 36.2 ± 10.4 ng/mL, 1.4 ± 0.7 hours, 4.6 ± 1.6 hour and 0.1642 respectively. The $C_{max}$, $t_{max}$, half-life of elimination ($t_{1/2}$) and the rate of elimination ($K_{el}$) of pregabalin of reference drug were40.3 ± 9.4 ng/mL, 1.1 ± 0.3 hours**,** 4.1 ± 3.6 hour and 0.0975 respectively.

**Table I:** Pharmacokinetic parameters following oral administration of PRELIN™ (test) and LYRICA™ (reference)

| Parameters | Test drug | | | | Reference drug | | | |
|---|---|---|---|---|---|---|---|---|
| | mean | SD | 90%CI | | mean | SD | 90%CI | |
| | | | Lower | Upper | | | Lower | Upper |
| AUC (ng/hr/mL) | 105.0 | 32.8 | 96.8 | 103.2 | 126.9 | 40.0 | 96. 8 | 103.2 |
| $C_{max}$ (ng/mL) | 36.2 | 10.4 | 97.0 | 102.9 | 40.3 | 9.4 | 97.6 | 102.4 |
| $T_{max}$ (hour) | 1.4 | 0.7 | 94.4 | 105.5 | 1.1 | 0.3 | 96.3 | 103.6 |
| half-life (hour) | 4.6 | 1.6 | 96.4 | 103.5 | 4.1 | 3.6 | 90.9 | 109.0 |
| kel | 0.1642 | 0.0655 | 95.9008 | 104.1 | 0.0975 | 0.0459 | 95.1 | 104.8 |

$AUC_{0\rightarrow 24h}$ = Area under the plasma concentration–time curve from zero hours to 24 hours; $C_{max}$= maximal plasma concentration; $t_{max}$= time for the maximal plasma concentration; $t_{1/2}$ = half-life; $K_{el}$= elimination rate constant.

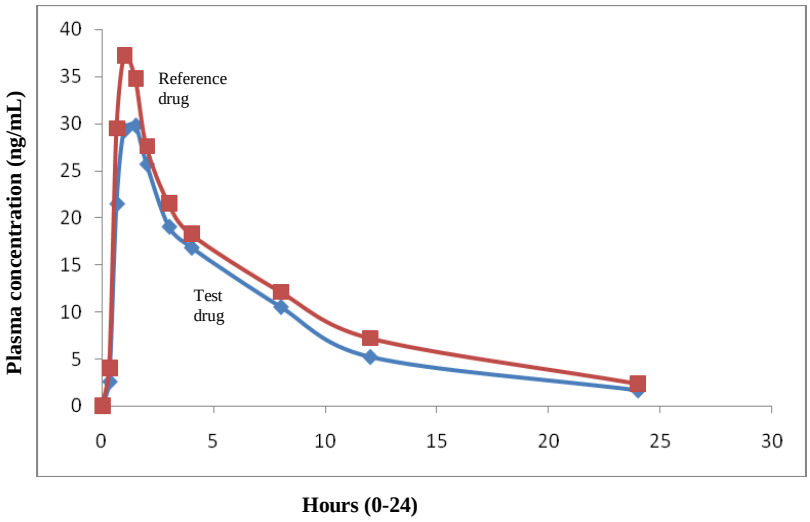


**Figure 1:** Mean plasma concentrations of pregabalin in 16 human volunteers

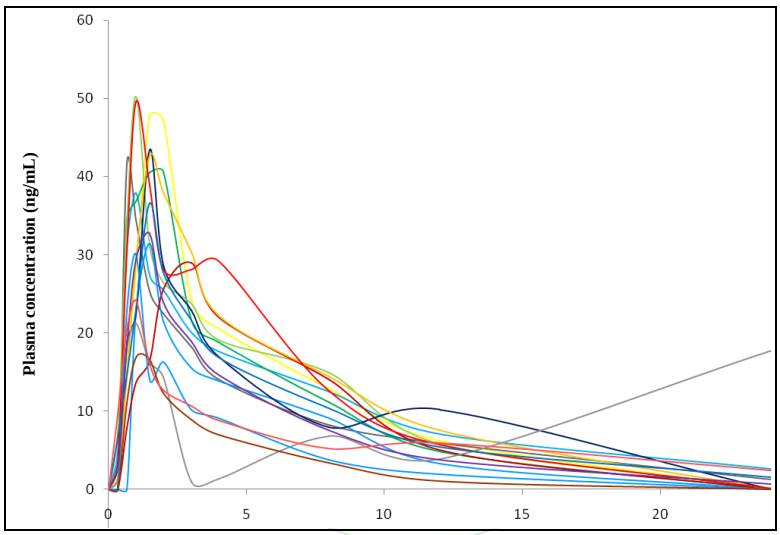


**Figure 2:** Data of individual volunteer (n=16) following administration of PRELIN™

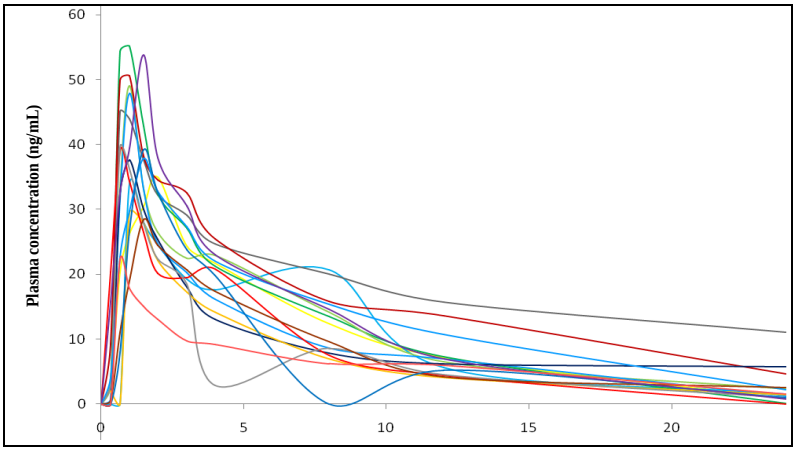


**Figure 3:** Data of individual volunteer (n=16) following administration of LYRICA™

## Tolerance

Single dose of pregabalin (150 mg) of both products were well tolerated by the volunteers.

## RESULT AND DISCUSSION

Establishing bioequivalence between a new generic formulation and its branded counterpart is essential to ensure no significant clinical differences exist in the rate

and extent of drug availability at the intended site of action. This investigation involved healthy adult male participants, each of whom received a single dose under fasting conditions. No adverse incidents or protocol deviations occurred during the study, and all volunteers completed the trial successfully and were discharged in good health.

The analytical method employed was both precise and sensitive for detecting pregabalin levels in plasma. The retention time was approximately 2.45 minutes, with a limit of detection (LOD) of 16 ng and a quantification limit (LOQ) of 54 ng. These values indicate that the method was suitable for conducting accurate pharmacokinetic assessments.

The main goal of this research was to compare the pharmacokinetic behavior and bioequivalence of two pregabalin formulations in healthy Bangladeshi males. The results demonstrated similar pharmacokinetic characteristics between PRELIN™ and LYRICA™. Both formulations showed efficient absorption from the gastrointestinal tract, with measurable plasma levels detected as early as 0.3 hours post-dose. Peak plasma concentrations occurred between 1.0 to 1.5 hours and declined steadily, yet pregabalin remained detectable for the entire 24-hour monitoring period. These findings are consistent with previously reported pharmacokinetic data.

The primary parameters evaluated—$AUC_{0\rightarrow 24}h$, $C_{max}$, $T_{max}$, half-life ($t_{½}$), and elimination rate constant ($K_{el}$)—are outlined in Table 1. These metrics are critical in determining the extent and rate of drug absorption and have direct implications on therapeutic performance. The relative bioavailability of PRELIN™ compared to LYRICA™ was calculated as 82.7%. The mean $C_{max}$, $T_{max}$, $t_{½}$, and $K_{el}$ values for the test formulation were 36.2 ± 10.4 ng/mL, 1.4 ± 0.7 h, 4.6 ± 1.6 h, and 0.1642 $h^{-1}$, respectively. In contrast, the corresponding values for LYRICA™ were 40.3 ± 9.4 ng/mL, 1.1 ± 0.3 h, 4.1 ± 3.6 h, and 0.0975 $h^{-1}$.

There were no major differences observed in the mean values or variability (standard deviation) of these parameters between the two products. The overall plasma concentration profiles were found to be closely aligned, suggesting comparable systemic exposure. Statistical analysis using ANOVA confirmed that there were no significant differences in pharmacokinetic outcomes between the test and reference formulations. Additionally, the 90% confidence intervals for the main parameters were near the FDA's accepted range of 80%–125%, although the AUC ratio for PRELIN™ fell slightly below the threshold.

## CONCLUSION

This study evaluated the bioequivalence of the generic formulation PRELIN™ (Drug International Ltd., Bangladesh) and the branded formulation LYRICA™ (Pfizer Laboratories) in healthy male volunteers. Using validated LC-MS/MS methods, pharmacokinetic parameters such as $AUC_{0\rightarrow 24}h$, $C_{max}$, $T_{max}$, $t_{½}$, and $K_{el}$were determined and compared. The results revealed that both formulations exhibited similar pharmacokinetic profiles, indicating efficient absorption and comparable systemic exposure. Although PRELIN™ demonstrated a slightly lower relative bioavailability (82.7%) compared to the reference product, the differences in key pharmacokinetic metrics were minimal and fell close to the accepted regulatory limits for bioequivalence. Importantly, both formulations were well tolerated, with no adverse effects reported. These findings support the conclusion that PRELIN™ is a viable and cost-effective alternative to LYRICA™, offering similar therapeutic potential for clinical use in managing conditions treated with pregabalin.

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