EJPMR, 2025, 12(11), 207-212 **Research Article** **Impact Factor 7.065**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

BIOEQUIVALENCE EVALUATION OF TWO EDOXABAN 60 MG TABLET FORMULATIONS IN HEALTHY INDIAN SUBJECTS: AN OPEN-LABEL, RANDOMIZED, TWO-PERIOD, SINGLE DOSE, CROSSOVER STUDY

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DOI: https://doi.org/10.5281/zenodo.17472559

How to cite this Article: Dr. Bhupesh Dewan*, Mr. Siddheshwar Shinde, Ms. Alisha Dabade. (2025). Bioequivalence Evaluation Of Two Edoxaban 60 Mg Tablet Formulations In Healthy Indian Subjects: An Open-Label, Randomized, Two-Period, Single Dose, Crossover Study. European Journal of Pharmaceutical and Medical Research, 12(11), 207–212.

Article Received on 03/10/2025 **Article Revised on 24/10/2025** **Article Published on 01/11/2025**

ABSTRACT

Objective: To evaluate the bioequivalence of two oral tablet formulations of edoxaban 60 mg in healthy Indian adults. **Method and material**: An open-label, randomized, two-treatment, two-sequence, two-period, single-dose crossover study was conducted under fasting conditions. Eligible subjects received a single 60 mg tablet of edoxaban, either the test formulation (Supexa-OD™ from Zuventus Healthcare Limited, India) or the reference formulation (Lixiana® from Daiichi Sankyo Europe GmbH, Germany). The two doses were separated by a 7-day washout period. Blood samples were collected up to 72 hours post-dose, and the plasma concentrations of edoxaban were detected using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{1/2}$, and K_{el} were determined. Bioequivalence was assessed by calculating the geometric least square (LS) mean ratios and corresponding 90% confidence intervals (CIs) for these parameters. Safety was evaluated by monitoring adverse events. **Results**: Forty subjects were randomized and completed the study. The pharmacokinetic parameters of the test formulation were similar to those of the reference. The 90% CIs of the geometric LS mean ratios of the test to reference for C_{max} (86.53-114.53%), AUC_{0-t} (100.87-115.43%), and AUC_{0-inf} (100.38-113.31) fell within the acceptable range of 80.00–125.00%. Both formulations were well tolerated, with no serious adverse events reported. **Conclusions**: Both formulations of edoxaban 60 mg tablet were bioequivalent and well-tolerated in healthy Indian adults under fasting conditions. These findings support their interchangeability in clinical practice.

KEYWORDS: Bioequivalence, Edoxaban, Factor Xa Inhibitors, Oral anticoagulant.

1. INTRODUCTION

Edoxaban is a novel, orally available, direct inhibitor of factor Xa approved for the prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (NVAF) and for the treatment of venous thromboembolism (VTE).[1] Edoxaban exerts its anticoagulant effect by selectively inhibiting activated clotting factor Xa, the serine protease responsible for the generation of thrombin.[2] Since its first approval in Japan in 2011, edoxaban has demonstrated efficacy and safety through multiple randomized clinical trials in NVAF and VTE patients.[3-7] Edoxaban has been granted regulatory approved in Japan,[8] the United States,[1] the European Union[9] and India.[10] It is also recommended by the American Society of Haematology, 2020[11] and the European Society of Cardiology, 2024[12] guidelines for patients at elevated thromboembolic risk.

Edoxaban has a rapid absorption after oral administration with a time to peak plasma concentration of 1-2 hours. It has an absolute oral bioavailability of 61.8%.[13] Absorption of Edoxaban is not affected by food.[14] It undergoes hepatic metabolism primarily via carboxylesterase 1 (CES1), and to a lesser extent, by cytochrome P450 3A4 (CYP3A4).[15] Edoxaban has a longer terminal elimination half-life of 10-14 hours,[1,4]

which sustains for up to 24 hours, allowing for once-daily (OD) dosing, unlike dabigatran[16] and apixaban,[17] which require twice-daily administration. It is primarily excreted by the kidneys and the hepatobiliary system.[13]

While the clinical pharmacokinetics, safety, and tolerability of edoxaban have been previously studied in Japanese and Caucasian populations,[14] data on the Indian population remain limited. Therefore, this study aims to compare the pharmacokinetic parameters and bioequivalence of the test formulation, edoxaban 60 mg tablet, with the reference formulation Lixiana® (Edoxaban 60 mg) tablets in healthy Indian adults under fasting conditions.

2. MATERIALS AND METHODS

2.1 Ethical Consideration

The Institutional Ethics Committee (Reg. No.: ECR/139/Inst/AP/2013/RR-19) and the Central Licensing Authority (BENOC No.: BE/ND/04/2023) reviewed and approved the study protocol and informed consent documents before the study initiation. All subjects provided written informed consent prior to enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013),[18] Good Clinical Practice Guidelines,[19] Bioavailability and Bioequivalence Guidelines,[20,21] Indian Council of Medical Research Guidelines,[22] and the New Drugs and Clinical Trials Rules, 2019, India.[23]

2.2 Study Design

This was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover, oral bioequivalence study (Study Registry No.: CTRI/2023/06/054295) in healthy adult subjects under fasting conditions. This study was carried out between June 2023 to July 2023 at Advity Research (P) Limited, Hyderabad (Reg. No.: BABE/2022/0103).

Subjects were randomly assigned to receive a single tablet of either the test (T) formulation Edoxaban 60 mg (Supexa-OD™; Zuventus Healthcare Limited, India) or the reference (R) formulation (Lixiana®, Daiichi Sankyo Europe GmbH, Germany), following an overnight fast of at least 10 hours before dosing in each study period. Randomization was conducted using a SAS® (version 9.4) generated schedule, assigning subjects to one of two sequences (T-R or R-T). A 7-day washout period was maintained to ensure the complete elimination of edoxaban and minimize potential carryover effects.

Study subjects were required to stay at the study facility for at least 11 hours prior to dosing and remained under supervision for a minimum of 48 hours post-dose. They fasted overnight for at least 10 hours, continuing for an additional 4 hours after drug administration. Following dosing, subjects remained in a seated or semi-recumbent position for 2 hours. A single oral dose of the assigned formulation was administered with 240±02 mL of water. Water intake was restricted to 1 hour before and after dosing, after which it was permitted *ad libitum*.

2.3 Study Population

The study enrolled healthy volunteers aged 18 to 45 years, with a body mass index (BMI) ranging from 18.5 to 29.9 kg/m^2 and a weight greater than 60 kg. Eligibility screening was conducted within 21 days prior to enrolment and included general medical history (such as prior clinical trial participation, blood donation history, and alcohol or tobacco use), along with demographic data, medical history, and a physical examination. Assessments included vital signs, electrocardiogram, chest X-ray, hematology, biochemistry, urinalysis, and serology tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and creatinine clearance (CrCl). Participants were also tested for HIV I and II, hepatitis B and C, and VDRL. Female participants were eligible if they were neither pregnant nor breastfeeding and agreed to use reliable contraception methods. Exclusion criteria included the use of any medications within 14 days prior to dosing, a history of malignancies, thrombotic or thromboembolic complications, gastrointestinal ulceration or bleeding, or brain, spinal or ophthalmic surgery within the last year. Other exclusions included hypersensitivity to edoxaban or any drugs in its class, clinically significant diseases, any condition that could interfere with the pharmacokinetics of the investigational product and positive urine test for drugs of abuse, history of drug use and/or alcoholism, and dehydration from diarrhea, vomiting or any other reason, within the 24 hours prior to study start. All volunteers provided written informed consent before participation.

2.4 Sample Collection and Analysis of Plasma Edoxaban

At each study period, a total of 25 blood samples (5.00 mL each) were collected from each subject. Sampling occurred at pre-dose (00.00 hours) and at 00.17, 00.33, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose. Samples were collected in vacutainers containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) during each study period. All samples were centrifuged at 3500 rpm for 10 minutes at 5°C within 45 minutes of collection. An aliquot of the separated plasma was transferred into two pre-labelled polypropylene tubes and stored at -70±15°C until transferred to the bioanalytical department.

Edoxaban sample analysis was performed using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method, adhering to good laboratory practice (GLP) principles.[24] Edoxaban was extracted from human plasma using a liquid-liquid extraction technique. Plasma concentrations were measured using a Shimadzu HPLC system (LC-40 Series) coupled with a Sciex 4500 triple quadrupole mass

spectrometer. A 0.2 mL plasma aliquot, containing the analyte and internal standard, underwent liquid-liquid extraction. The extracted supernatant (10 µL) was injected into the system, which was equipped with a Phenomenex C18 column (100 × 4.6 mm, 5 µm, 110 Å). The mobile phase consisted of 0.1% formic acid in a 70:30 ratio, with a flow rate of 0.9 mL/min. Detection was conducted in positive-ion mode using electrospray ionization (ESI) and multiple reaction monitoring (MRM). The MRM transitions were m/z 548.200 → 366.300 for edoxaban and m/z 554.200 → 372.400 for the internal standard (Edoxaban-D6). The method had a linear range of 797.269 ng/mL to 4.000 ng/mL for edoxaban.

2.5 Pharmacokinetic parameters

The primary pharmacokinetic parameters calculated were peak plasma concentration (C_{max}), area under the concentration-time curve from time zero to the last time point (AUC_{0-t}) calculated by linear trapezoidal method, and total area under the concentration-time curve from time zero extrapolated to infinity (AUC_{0-inf}). Secondary pharmacokinetic parameters included time to peak concentration (T_{max}), elimination rate constant K_{el}, elimination half-life ($t_{1/2}$) calculated by Ln(2)/K_{e1}, and % extrapolation ($AUC_{\_\% Extrapolation}$) calculated as, [AUC_{t-inf} - AUC_{0-t}] × 100/AUC_{t-inf}. For pharmacokinetic and statistical analyses, values below the lower limit of quantification (LLOQ) were treated as zero, while missing or non-reportable values were excluded from parameter calculations.

2.6 Statistical Methods

Bioequivalence was assessed in 40 subjects, considering a 23% intra-subject variability for C_{max}, a geometric LS mean ratio (T/R) of 95% -105.3%, 90% power, and a 0.05 significance level. Statistical analysis of ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) for edoxaban was performed using SAS® Version 9.4 (SAS® Institute Inc., USA). A PROC GLM analyses of variance (ANOVA) model was applied, with treatment as the main effect, and it was tested at 0.05. A two one-sided test was applied to calculate 90% confidence intervals (CIs) for C_{max}, AUC_{0-t}, and AUC_{0-inf} using ln-transformed data. Bioequivalence was confirmed if the 90% CI fell within the acceptance range of 80.00%–125.00%.

2.7 Safety Assessments

The safety of test and reference formulation was evaluated through adverse event (AE) monitoring. AEs noted by the investigator or reported by the subjects were recorded. Additionally, results from physical examinations, clinical laboratory tests, and vital signs (blood pressure, radial pulse rate, respiratory rate, and body temperature) were assessed at various time points throughout the study. Biochemical parameters were measured pre-dose in both periods, including prothrombin time (PT) and activated partial thromboplastin time (aPTT). Post-study safety evaluation of laboratory parameters [haematology, biochemistry, PT, and aPTT tests] was evaluated in all subjects.

3. RESULTS

3.1 Demographic Characteristics

A total of 40 eligible male subjects were enrolled and randomized, with a mean age of 34 ± 5.67 years (range: 21–44) and a BMI of 25.6 ± 2.39 kg/m² (range: 19.2–29.9). Since all subjects completed the study, pharmacokinetic and statistical analyses were performed on all 40 participants across both study periods to assess bioequivalence, as shown in Figure 1.

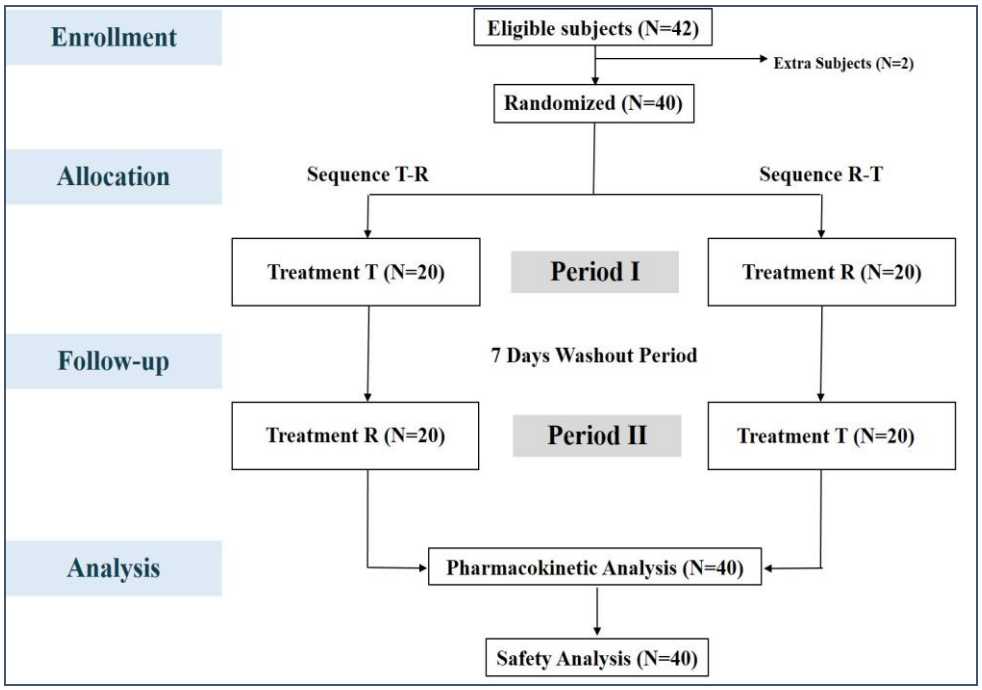

Figure 1: Disposition of subjects.

3.2. Bioanalytical Method Validation

The bioanalytical method for quantifying edoxaban in human plasma (4.000–797.269 ng/mL) was validated using weighted $1/X^2$ regression, with an LLOQ of 4 ng/mL. Linearity was confirmed with a goodness-of-fit value exceeding 0.99, correlation coefficients (r) of ≥0.99, and regression coefficients (r^2) of ≥0.98, meeting regulatory standards. The recovery rates were 92.0% for edoxaban and 95.8% for the internal standard. Stability assessments showed that edoxaban remained stable in plasma for 2 hours and 45 minutes at room temperature, 2 hours and 37 minutes at temperatures below 10°C, and after five freeze-thaw cycles. Additionally, autosampler stability was maintained for 65 hours and 30 minutes, while bench-top stability was confirmed for 21 hours and 38 minutes.

3.3 Pharmacokinetics and Statistical Evaluation

The change in edoxaban plasma concentrations from time 0–72 h post-dose is represented in Figure 2. Edoxaban was rapidly absorbed, with mean peak plasma concentrations of 305.87 ng/mL for the test formulation at a mean time of 1.25 hours. For reference, the corresponding values were 302.57 ng/mL at a mean time of 1.00 hours. The total drug exposure over 72 hours was similar between the two formulations. The AUC_{0-t} values were 1877.29 ng.hr/mL for test formulation and 1722.27 ng.hr/mL for the reference. A summary of the PK parameters of edoxaban is shown in Table 1.

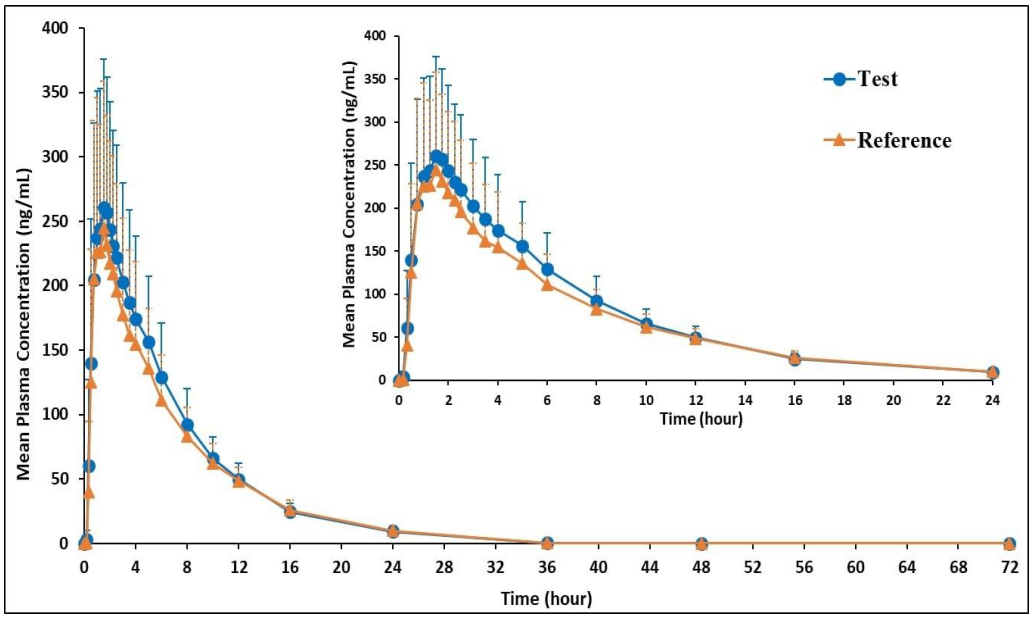

Figure 2: Linear plasma Edoxaban concentration versus time curves following administration of test and reference formulation over 72 hours. ***Inset represents concentration-time profiles for the first 24 hours. Data represents the mean value, and error bars represent the standard deviation (SD).***

Table 1: Pharmacokinetic parameters of Edoxaban.

Parameters	Arithmetic mean ± SD (%CV) (N = 40)	
	Test formulation	Reference formulation
C_{max} (ng/mL)	305.87 ± 121.537 (39.74)	302.57 ± 122.193 (40.38)
AUC_{0-t} (ng.hr/mL)	1877.29 ± 538.649 (28.69)	1722.27 ± 465.519 (27.03)
AUC_{0-inf} (ng.hr/mL)	1937.48 ± 535.433 (27.64)	1799.04 ± 456.000 (25.35)
T_{max} (h) *	1.25 (0.50-5.00)	1.00 (0.50-3.00)
$t_{1/2}$ (h)	4.86 ± 1.157 (23.83)	5.30 ± 1.089 (20.57)
K_{el} (1/h)	0.15 ± 0.029 (19.35)	0.14 ± 0.031 (22.40)
$AUC_{\_\%Extrap\_obs}$ (%)	3.52 ± 2.472 (70.28)	4.63 ± 2.745 (59.28)

Values are presented in mean ± SD and median (range)
CV: covariance, SD: standard deviation,
* *For T_{max}: median (Min-Max)*

The ln-transformed geometric LS mean ratios (90% CIs) for $C_{max,}$ $AUC_{0-t,}$ and AUC_{0-inf} were 99.55% (86.53-114.53), 107.90% (100.87-115.43), and 106.65 (100.38-113.31), respectively, as given in Table 2. The $C_{max,}$ $AUC_{0-t,}$ and AUC_{0-inf} values for both test and reference formulations were similar, with 90% CIs of the geometric LS mean ratios falling within the predefined 80.00–125.00% bioequivalence criterion stipulated by regulatory agencies. The intra-subject coefficient of variation (ISCV) was 38.49% for C_{max} demonstrating

high variability (>30%). Analysis of variance for ln-transformed PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) showed no statistically significant effect of variation due to treatment.

Table 2: Ratio analysis and 90% confidence intervals.

PK Parameters	Geometric LS mean (N=40)					
	Test (T)	Reference (R)	T/R ratio (%)	ISCV (%)	Power (%)	90% CI
LnC_{max} (ng/mL)	274.87	276.11	99.55	38.49	83.79	86.53-114.53
$LnAUC_{0-t}$ (ng.hr/mL)	1794.56	1663.11	107.90	18.02	99.98	100.87-115.43
$LnAUC_{0-inf}$ (ng.hr/mL)	1860.59	1744.58	106.65	16.17	>99.99	100.38-113.31

CI: confidence interval, ISCV: intra-subject coefficient of variance, LS: least square

3.4 Safety Results

There were no reports of death or serious unexpected adverse events. No clinically significant changes were observed in physical examinations, laboratory test results, or vital signs attributable to edoxaban. Pre-dose assessments confirmed that prothrombin time (13.56 and 13.68 sec) and activated partial thromboplastin time (32.39 and 32.41 sec) remained within the normal range even after treatment, suggesting no increased risk of bleeding following the 7-day washout period. Post-study safety evaluations of laboratory parameters, including haematology and biochemistry, confirmed that all values remained within the normal range. Only one adverse event (AE), mild abdominal pain, was reported during period 1 and resolved on the same day.

4. DISCUSSION

This study marks the first bioequivalence evaluation of edoxaban conducted in India. It compares the pharmacokinetic parameters and bioavailability of two edoxaban 60 mg tablet formulations. The sample size was adequate to assess the pharmacokinetic profile of both formulations. No significant differences were observed among the participants. The study included only male subjects, as sex has no significant impact on edoxaban's pharmacokinetics.[15] Therefore, similar results are expected in females.

Edoxaban demonstrated a rapid absorption, with a T_{max} of 1.25 hours for the test formulation and 1.00 hours for reference. The observed elimination half-life ($t_{1/2}$) was 4.86 hours and 5.3 hours for test and reference formulations, respectively, indicating that the 7-day washout period was adequate for this study. The pharmacokinetic parameters of both test and reference formulations were comparable. The C_{max}, AUC_{0-t}, and AUC_{0-inf} values for the test formulation closely aligned with those of the reference formulation. In addition, the ratio of AUC_{0-t} to AUC_{0-inf} of these two formulations was over 80%, suggesting that the time covered by blood sampling was sufficient to adequately describe the plasma concentration-time profile in this study.

The 90% CIs for the geometric least-square mean ratios of C_{max} (99.55%), AUC_{0-t} (107.90%), and AUC_{0-inf} (106.65%) fell within the acceptable range of 80.00–125.00%, confirming bioequivalence between the two formulations as per regulatory guidelines. Furthermore, these findings were consistent with previously reported values in the literature,[2] where mean C_{max} ranged from 256-293 ng/mL, AUC_{0-t} from 1753-2089 ng.hr/mL, and T_{max} from 1.02-1.5 hours.

Edoxaban tablets were well tolerated among healthy Indian subjects. No deaths, serious adverse events, or study discontinuations were reported. The only observed adverse event, mild abdominal pain, was consistent with the known safety profile of edoxaban[1,4,8] and resolved within the same day. These results confirm the comparable safety of both edoxaban 60 mg tablet formulations.

5. CONCLUSION

This study confirms the bioequivalence of the test formulation, Supexa-OD™ of Zuventus Healthcare Limited, India to the reference formulation, Lixiana® under fasting conditions. Both formulations demonstrated excellent tolerability in the Indian population. These findings support their interchangeability in clinical practice.

ACKNOWLEDGEMENT

None.

ETHICAL STATEMENT

The study was approved by the CDSCO, India and the Institutional Ethics Committee of the study centre. The trial was conducted in compliance with the Guidelines for Good Clinical Practice, and the Declaration of Helsinki principles.

CONFLICT OF INTEREST

There are no conflicts of interest.

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