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Bioequivalence Studies of Two Formulations of Rivaroxaban 10 Mg Coated Tablets under Fasting Conditions and 20 Mg Coated Tablets under Fed and Fast Conditions and its Pharmacokinetic Comparison in Healthy Subjects

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Abstract

Justificative: This trial was conducted in order to register a new generic product of Rivaroxaban.

Objective: To evaluate the bioequivalence of rivaroxaban formulations manufactured by Eurofarma Laboratórios S/A and the reference drug, Xarelto (Bayer) under fasting and fed conditions.

Methods: Three randomized, open label, balanced, 2 treatments, 4 periods, 2 sequences, single dose, full replicate, crossover studies in 48 healthy adult human subjects under fed and fasting conditions for rivaroxaban 10 mg and 20 mg. Rivaroxaban concentrations in plasma were determined using a validated HPLC-MS/MS method.

Results: The geometric mean ratio (90%CI) of the test/reference for rivaroxaban was 93.05% to 102.69% for AUC0-t in 10 mg coated tablet under fasting conditions, 98.22% to 108.47% in 20 mg coated tablet under fasting conditions and 100.58% to 107.32% in 20 mg coated tablet under fed conditions. The AUC0-inf were 92.82% to 102.03% in 10 mg coated tablet under fasting conditions, 96.52% to 107.73% in 20 mg coated tablet under fasting conditions and 100.53% to 107.12% in 20 mg coated tablet under fed conditions. The Cmax values for 10 mg coated tablet were 90.53% to 103,07% and 97.52% to 109.87% and 99,40% to 106,15% in 20 mg coated tablet under fasting and fed conditions, respectively. No any serious or significant adverse event was observed during the entire course of the studies in all conditions.

Conclusion: Rivaroxaban 10 mg and 20 mg manufactured by Eurofarma Laboratórios S/A are statistically bioequivalent, to

the reference drug Xarelto® (Bayer), according to their rate and extension of absorption.

Keywords: Rivaroxaban; Bioequivalence; Pharmacokinetics; HPLC MS; Factor Xa inhibitor.

List of abbreviations: ACS Acute coronary syndrome (ACS); ASA Acethyl Salicilic Acid (ASA); Bcrp breast cancer resistance protein; b.i.d. twice-daily; BMI body mass index; Cmax maximum concentration; DVT deep vein thrombosis (DVT); LC-MS-MS LC-MS/MS Liquid Chromatography Tandem Mass Spectrometry m/zmass charge ratio (m/z); MRM multiple reactions monitoring; NOACs New oral anticoagulants; PE pulmonary embolism (PE); P-gp P-glycoprotein (P-gp); q.d. once-daily

Introduction

Acute coronary syndrome (ACS) is caused by thrombosis in the coronary arteries. Arterial thrombosis involves both platelet aggregation and the activation of the coagulation cascade, providing the rationale for anticoagulant therapy in addition to antiplatelet therapy for secondary prevention of cardiovascular events in patients with ACS. Currently, triple antithrombotic therapy with warfarin, Acethyl Salicilic Acid (ASA) and clopidogrel is only recommended in patients at low risk of bleeding. These limitations include multiple drug-drug and food-drug interactions and unpredictable responses that necessitate routine coagulation monitoring and dose adjustments to ensure that patients maintain an appropriate anticoagulation intensity. In addition, anticoagulants are used in the pharmacotherapy of several cardiovascular diseases, such as deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Novel oral anticoagulants have been developed in recent years in an attempt to overcome some of the limitations associated with traditional agents (such as unfractionated heparin, low molecular weight heparins, fondaparinux and the vitamin K antagonists) [2]. These limitations have prompted the development of target-specific oral anticoagulants that directly inhibit single enzymes in the coagulation pathway, such as Factor Xa or thrombin [2].

Rivaroxaban, a rapid-onset drug, targets free and clot bound Factor Xa in the prothrombinase complex. This drug results in maximum plasma concentration 2-4 hours after administration and presents high bioavailability (80% to 100%) as a 10-mg tablet [3].

The metabolism and excretion of rivaroxaban involve cytochrome P450 3A4 (CYP3A4) and 2J2 (CYP2J2), CYP-independent mechanisms, and P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp) (ABCG2). Rivaroxaban did not interact with midazolam (CYP3A4 probe substrate). A significant increase in rivaroxaban exposure was demonstrated with the strong CYP3A4, P-gp/Bcrp (ABCG2) inhibitors (and potential CYP2J2 inhibitors) ketoconazole (158% increase [95% CI 136%, 182%] for a 400 mg once daily dose) and ritonavir (153% increase [95% CI 134%, 174%]) [4].

Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5–9 h in healthy young subjects and 11–13 h in elderly subjects [5]. Approximately two-thirds of the rivaroxaban dose is metabolized in the liver, of which one-half then excreted via the kidneys and the other-half via the hepatobiliary route [6].

The antithrombotic effect of rivaroxaban, as measured by prothrombin time prolongation or Factor X activity, is dependent on plasma concentration and systemic exposure [7].

Rivaroxaban bioavailability ranges from 66%-100%, depending on the dose and whether or not the dose is administered with a meal. The drug requires administration with food to achieve similar bioavailability with doses greater than 10 mg and achieves maximal plasma concentrations ~3 hours after administration [8].

After an oral dose of 10 mg rivaroxaban, the metabolite profile in human plasma showed unchanged rivaroxaban concentration [9].

Rivaroxaban was initially approved in Canada in 2008 for the prevention of thromboembolic events in patients undergoing total hip or knee arthroplasty [10]. Since then, rivaroxaban, an oral direct inhibitor of factor Xa, has been used to prevent stroke in patients with nonvalvular atrial fibrillation (NVAF) and treatment and prevention of thromboembolic diseases around the world [11].

Rivaroxaban exposure is considerably increased by drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 (CYP) 3A inhibitors (e.g. ketoconazole) [12].

A single center, randomized, open label, 2 way crossover study of effect of food on rivaroxaban 20 mg has demonstrated that food increases the bioavailability of rivaroxaban: AUC was increased by 39% and Cmax by 76% [13].

Six independent, single-dose, cross-over studies were performed in healthy male subjects (between 13 and 24 subjects were enrolled in each study) to determine the pharmacokinetics, safety, and tolerability of rivaroxaban under fasting and fed conditions. Independent of food and formulation, pharmacokinetic parameters of doses up to 10 mg rivaroxaban were dose proportional and had high oral bioavailability (≥ 80%). Under fasting conditions, pharmacokinetic parameters of 15 mg and 20 mg rivaroxaban increased with dose but were less than dose proportional. However, when taken with food, high bioavailability (≥ 80%) of these doses was achieved independent of formulation [14].

Generic prescribing is associated with improved medication adherence. A q.d. dosing schedule is associated with increased adherence and persistence to cardiovascular therapies. In addition, such feature appears to be responsible for the significantly lower discontinuation of q.d. NOACs compared with b.i.d. NOACs in large, real-world dataset of patients with AF. Reports about adherence to NOAC therapy are limited. At the same time, in countries with centralized health systems, as in Brazil (SUS, the National Health System), the importance of generic drugs is based on maintenance of supply by government due to long-term negotiation with pharmaceutical companies, at lower costs than branded products and the competition from multiple market players (industry, distribution).

Materials and Methods

Study Formulations

The test products were 10 mg Rivaroxaban coated tablet and 20 mg Rivaroxaban coated tablet, both developed by Eurofarma Laboratórios S.A., Brazil. The reference products were Xarelto®, 10 mg Rivaroxaban coated tablet and Xarelto®, 20 mg Rivaroxaban coated tablet, both manufactured by Bayer Pharma AG Leverkusen, Germany and distributed by Bayer S.A., Brazil.

Ethics Considerations

All subjects were given a talk, intended to explain in detail the study; all questions were solved, so they could freely decide to participate in the study. After that, each one of the volunteers singed the Informed Consent. Both study protocol and Informed Consent template were approved by the Siddhant Independent Ethics Committee, Ahmedabad, India.

Study 10 mg Rivaroxaban (fasting)

Forty-eight healthy, adult, human subjects (24 from each gender) aged between 19 and 44 years, having body mass index (BMI) between 18.99 kg/m² and 29.50 kg/m² were enrolled according to the inclusion and exclusion criteria. Forty-two subject samples were considered for bioequivalence, due to drop out or exclusions.

The volunteers remained fasting at least 10 hours before drug administration and for at least 4 hours post dose in each study period. All subjects have received a coated tablet containing 10 mg of Rivaroxaban of either Test or Reference product, administered

orally in a single dose, with 200 mL of regular water. Drug administrations were performed around 9 a.m. according to the randomization list and under open-label conditions.

Study 20 mg Rivaroxaban (fasting)

Forty-eight healthy, adult, human subjects (24 from each gender) aged between 22 and 44 years, having body mass index (BMI) between 19.00 kg/m² and 29.66 kg/m² were enrolled according to the inclusion and exclusion criteria. Forty-four subject samples were considered for bioequivalence, due to drop out or exclusions.

The volunteers remained fasting at least 10 hours before drug administration and for at least 4 hours post dose in each study period. All subjects have received a coated tablet containing 20 mg of Rivaroxaban of either Test or Reference product, administered orally in a single dose, with 200 mL of regular water. Drug administrations were performed around 9 a.m. according to the randomization list and under open-label conditions.

Study 20 mg Rivaroxaban (fed)

Forty-eight healthy, adult, human subjects (24 Male + 24 Female) aged between 19 and 44 years, having body mass index (BMI) between 19.06 kg/m² and 29.89 kg/m² were enrolled according to the inclusion and exclusion criteria. Forty-four subject samples were considered for bioequivalence, due to drop out or exclusions. The volunteers remained fasting at least 10 hours prior to consuming a standardized breakfast, which was started by subject 30 minutes before dosing and for at least 4 hours post dose in each study period. All subjects have received a coated tablet containing 20 mg of Rivaroxaban of either Test or Reference product, administered orally in a single dose, with 200 mL of regular water. Drug administrations were performed around 9 a.m. according to the randomization list and under open-label conditions.

Study Design

The three studies were single-center, open-label, randomized, 4 periods, 2 sequences, with 2 treatments (T and R) being balanced by two (2) treatment sequences (RTRT and TRTR). All studies were conducted at Accutest Research Laboratories (I) Pvt. Ltd. (Unit-I), Ahmedabad, India, a center certified by FDA, EMA, ANVISA and other local as well as international health authorities.

After screening the formulations were administered as a single dose orally followed by blood sampling for up to 48.00 hours from dosing and a washout period of at least 07 days.

Blood Sampling

A total of 20 blood samples [4 mL per sample] were collected in K2-EDTA Vacutainer, in each study period per subject.

Blood samples were obtained prior to dosing (baseline) and 0.50, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.50, 5.00, 6.00, 9.00, 12.00, 24.00, 36.00 and 48.00 hour post-dose.

Centrifugations of the samples were done within 1 hour after the blood sample collection of respective time point. Following centrifugation under refrigeration at 3500 RPM for 10 minutes at 5°C ± 3°C, the plasma was transferred to appropriate size biological sample storage vials (previously labeled with subject number, nature of sample (analytical or control sample), study code, period number and sample number), in duplicate (one aliquot as control samples and one aliquot for analysis; the aliquot for analysis contained approximately 1.5 ml of plasma).

The vials containing plasma samples were kept in the pre-labeled vial-holding racks. The vial holding racks were stored in a deep freezer maintained at -20°C ± 5°C.

Determination of Rivaroxaban plasma concentrations

Method Validation

The bioanalytical method was developed and standardized for the quantification of Rivaroxaban in human plasma by LC-MS/MS using Rivaroxaban D4 as internal standard, and was fully validated meeting all the criteria for acceptability of selectivity, calibration curve, precision, accuracy, carry-over, matrix effect, recovery, and stability tests, according to both FDA and Anvisa's guidelines for bioanalytical method validation, using standard operating procedures of an accredited facility.

Linearity

Linearity was determined to assess the ability of the method relates adequately the analyte concentration with the instrumental response. The straight-line equation was obtained and applied to the peak response (area ratios of plasma analyte vs internal standard): y = a + bx [weighted 1/x*x], where "y" is the response and "x" is the analyte concentration. Linearity was found for concentrations from 2.00 to 1,000.00 ng/mL.

The samples concentration calculation was based on the construction of a calibration curve for analyte with the Analyst version 1.6.1 software data system. The function applied to the different samples of the calibration curve was calculated by a weighted linear regression system using the relationship between the area of the analyte and the internal standard area (response) of the respective chromatograms and this function was validated according to the current legislation prior to evaluation of other parameters.

Precision and Accuracy

Low Limit of Quantification (LLOQ) established by the method was 2.00 ng/mL and QC samples validated were 6.00, 50.00, 360.00 and 780.00 ng/mL.

Stability

Stability analysis was carried out with spiked plasma (6 and 780 ng/mL), subjected to appropriate condition to assure stability after 5 freeze-and-thaw cycles, short-term (15 h) at room temperature, as well as 50 h autosampler (10 °C), 6 h processed sample stability at room temperature and 135 days of long-term stability at -20°C.

Chemicals and Standard Solutions

Chemicals included ultrapure water from Millipore purification system, Acetonitrile HPLC grade from Merck, Methanol HPLC grade from Merck, Glacial acetic acid from Merck and Chloroform HPLC grade from Spectrochem. The reference material used Rivaroxaban (analyte) and Rivaroxaban D4 (internal standard) were purchased from Clearshynth Labs Ltd (India).

Standard stock solutions were prepared in chloroform followed by methanol and working solutions in Methanol/Water (8/2; v/v). Mobile phase consisted in 0.1% Acetic Acid Buffer/Acetonitrile (30/70; v/v).

Plasma Sample Extraction

Plasma samples (100 µL) were vortex-mixed for 10 seconds. The next step was to add 0.5 mL of water and vortex-mix for 30 seconds, followed by centrifugation (12,000 rpm) for 5 minutes at 10°C. Samples were submitted to Solid Phase Extraction through Phenomenex Strata-X cartridges (30 mg/ 1 mL). The conditioning and equilibration were performed by passing 1 mL of Methanol followed by 1 mL water. Then, samples were loaded and they were drained by applying pressure not more than 2 psi. They were washed with 1 mL of water followed by 1 mL of 20% (v/v) methanol and eluted with mobile phase.

Chromatographic Conditions

HPLC separation was performed using a Hypersil GOLD (100 x 4.6mm), 5µ column. The isocratic elution was performed using a binary pump (Shimadzu), and the mobile phase was composed by Buffer / Acetonitrile (70/30 v/v). The column temperature was maintained at 30°C. The injection volume was 3 µL and run time of 5 min.

Mass-Spectrometric Conditions

The compounds were extracted from plasma samples and quantified by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) using an API 5500 (MDS Sciex), equipped with positive electrospray ionization ion source, and detecting the analyte and internal standard (IS) using multiple reactions monitoring (MRM) with the transitions of mass charge ratio (m/z) 436.4>145.1, and 440.2>145.1 respectively. The total run time used of 5 minutes was sufficient to elute the compounds of interest and leave the column free of matrix interferences.

The parameters of the bioanalytical method used are described in Table 1.

Table 1: Summary of the bioanalytical method

Validation	
Analyte	Rivaroxaban
Internal standard	Rivaroxaban D4
Biological matrix	human plasma
Anticoagulant	K2-EDTA
Linearity	2.00 a 1,000.00 ng/mL
Calibration Curve equation	$y = a + bx\ (1/x^2)$
Lower Limit of Quantification (LLQC)	2 ng/mL
Low Quality Control (LQC)	6 ng/mL
Medium Quality Control (M1QC)	50 ng/mL
Medium Quality Control (MQC)	360 ng/mL
High Quality Control (HQC)	780 ng/mL
Quantification parameter	Response (analyte area/PI area)
Stability	
Post-processing stability time	50 hours at 10°C and 6 hours at room temperature
Freeze/thaw cycles	5 cycles
Short term stability time	15 hours
Long term stability time	135 days

A simple, high sensitive, specific, rugged, and reproducible LC-MS/MS method for the determination of rivaroxaban in human plasma was developed and validated. The validation proved to be robust in terms of selectivity, linearity, precision, accuracy and stability for quantifying rivaroxaban for the proposed bioequivalence trials.

Results

Study Population

The three studies enrolled 48 healthy, adult, human subjects (24 Male + 24 Female) each one. Forty-two subjects were assessed for bioequivalence in the 10 mg formulation fasting study and 44 were considered in the 20 mg fasting and fed studies. Details of population data are presented in Table 2.

Table 2: Population Data

Parameters(Units)	10 mg Fasting condition	20 mgFasting condition	20 mgFed condition
N	42	44	44
Age (y)			
Mean	35.31	34.95	33.84
Min-Max	19-44	24-44	19-44
BMI (kg/m^3)			
Mean	24.1	24.57	25.84
Min-Max	18.99-29.50	19.00-29.61	19.06-29.89

Pharmacokinetics and Statistical Analysis

Pharmacokinetics parameters obtained from the two bioequivalence studies are presented in Tables 3 to 5.

Table 3: PK parameters in the fasting condition (for rivaroxaban 10 mg coated tablets)

Pharmacokineticsparameters	**Rivaroxaban Eurofarma(Test) ***	**Xarelto®(Reference) ***
T_{max} (h)	2.584 ± 1.086	2.398 ± 1.143
C_{max} (ng.ml-1)	192.362 ± 61.079	199.394 ± 63.257
AUC_{0-t} (ng.h.ml-1)	1502.812 ± 488.717	1542.549 ± 513.359
AUC_{0-inf} (ng.h.ml-1)	1567.937 ± 493.027	1614.618 ± 516.961
AUC_{0-t} /AUC0-inf	95.658 ± 3.606	95.267 ± 3.370

* Arithmetic Mean ± SD

Pharmacokineticsparameters	**Rivaroxaban Eurofarma(Test) ***	**Xarelto®(Reference) ***
T_{max} (h)	2.649 ± 0.955	2.422 ± 0.951
C_{max} (ng.ml-1)	287.690 ± 104.825	276.922 ± 101.977
AUC_{0-t} (ng.h.ml-1)	2597.106 ± 975.728	2529.166 ± 974.318
AUC_{0-inf} (ng.h.ml-1)	2687.667 ± 980.430	2655.544 ± 1021.939
AUC_{0-t} /AUC0-inf	96.289 ± 4.785	95.386 ± 7.336

Table 4: PK parameters in the fasting condition (for rivaroxaban 20 mg coated tablets)

* Arithmetic Mean ± SD

Pharmacokineticsparameters	Rivaroxaban Eurofarma(Test) *	Xarelto®(Reference) *
T_{max} (h)	4.333 ± 0.696	4.063 ± 1.098
C_{max} (ng.ml-1)	421.577 ± 81.028	410.754 ± 81.327
AUC_{0-t} (ng.h.ml-1)	3354.001 ± 832.743	3223.041 ± 777.146
AUC_{0-inf} (ng.h.ml-1)	3401.921 ± 827.393	3272.785 ± 770.506
AUC_{0-t} /AUC0-inf	98.474 ± 1.367	98.359 ± 1.400

Table 5: PK parameters in the fed condition (for rivaroxaban 20 mg coated tablet)

* Arithmetic Mean ± SD

Figure 1 shows the mean curves of plasma concentrations of Rivaroxaban 10 mg coated tablet in fasting conditions (reference and test drugs) versus time for the 42 subjects. Figure 2 and 3 show mean curves of plasma concentrations of Rivaroxaban 20 mg coated tablet in fasting and fed conditions, respectively.

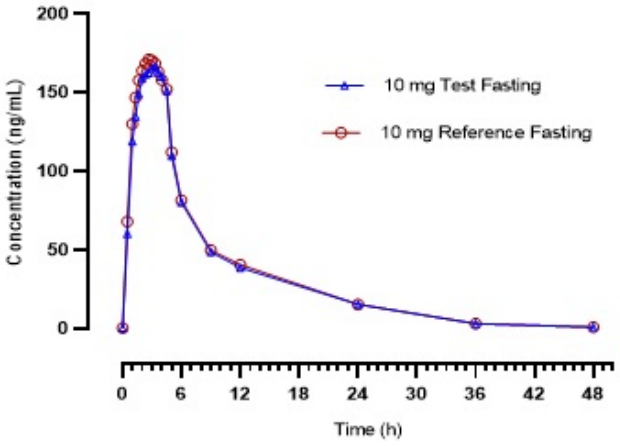


Figure 1: Mean plasma concentrations of 10 mg rivaroxaban under fasting conditions

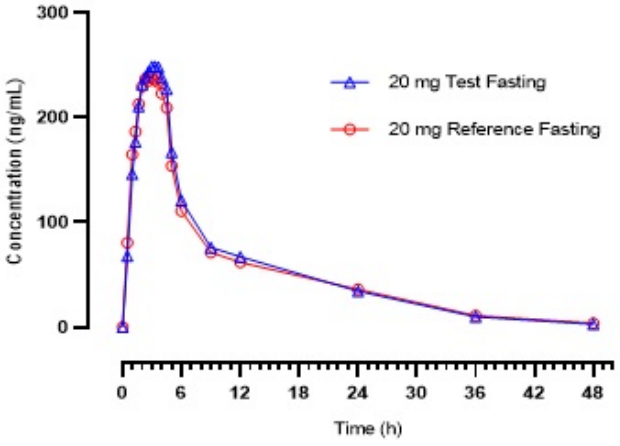


Figure 2: Mean plasma concentrations of 20 mg rivaroxaban under fasting conditions

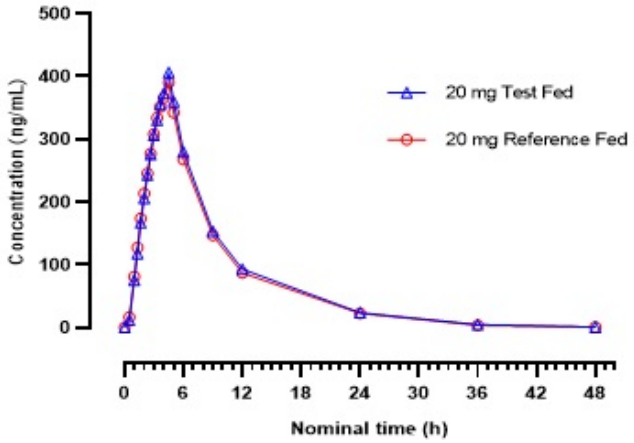


Figure 3: Mean plasma concentrations of 20 mg rivaroxaban under fed conditions

Tolerability/ Safety Analysis

All the formulations were well tolerated. No any serious or significant adverse event was observed during the entire course of both studies. All events were solved during study period.

During the 10 mg fasting study a total of 2 adverse events were reported. Both were moderate in severity, unlikely related to study medication and they were resolved.

During the 20 mg fasting study a total of 2 adverse events were reported. One adverse event was moderate in severity, unrelated to study medication and one AE was moderate in severity, possibly related to study medication and both AE were resolved.

Total of 3 adverse events were reported during the 20 mg fed study. From the reported AEs, 2 AEs were moderate in severity, related to study medication and 1 AE was mild in severity, unlikely related to study medication and they were resolved.

Discussion

All studies were planned and performed under Good Clinical and Laboratory Practices (GCP and GLP) guidelines, obtaining Cmax, AUC0-t and AUC0-inf, which values of confidence interval (90%) were within acceptable limit for ratio between geometric averages of test and reference products according to current legislation (80 to 125%) [15].

The performance of present method was comparable to other previous related using LC-MS techniques 16, showing a low enough LLOQ (2 ng/mL), an appropriate linear range (2-1000 ng/mL), and appropriate QCs covering all the range of observed values. The chosen matrix, K2-EDTA plasma, proved to be adequate, showing low matrix effect and a consistent and precise matrix factor typically about 1.2, and an IS normalized factor typically about 1.0, as expected when one work with deuterium labeled analogue compound.

Table 6 summarizes mean values for PK parameters for all studies. It is possible to notice that Tmax and Cmax are impacted by fed condition for Rivaroxaban 20 mg, Tmax and Cmax obtained were a little less than double of those obtained from 20 mg fasting study, what is extensively reported in the literature [16-18].

Food condition	Parameters	90% CIupper limit S_{WT}/S_{WR}	Geometric Mean Ratio	90% CI for adjusted GMR
10 mgFasting	AUC_{0-t}	1.4550	97.7506	93.0477 - 102.6911
n = 42	AUC_{0-inf}	1.4746	97.3167	92.8186 - 102.0328
	C_{max}	1.4991	96.5959	90.5304 - 103.0678
20 mgFasting	AUC_{0-t}	1.3998	103.2205	98.2211 - 108.4743
n = 44	AUC_{0-inf}	1.2372	101.9761	96.5231 - 107.7371
	C_{max}	1.1981	103.5107	97.5196 - 109.8697
20 mg Fed	AUC_{0-t}	1.3395	103.8950	100.5793 - 107.3199
n = 44	AUC_{0-inf}	1.2915	103.7729	100.5310 - 107.1193
	C_{max}	1.0559	102.7196	99.4010 - 106.1489

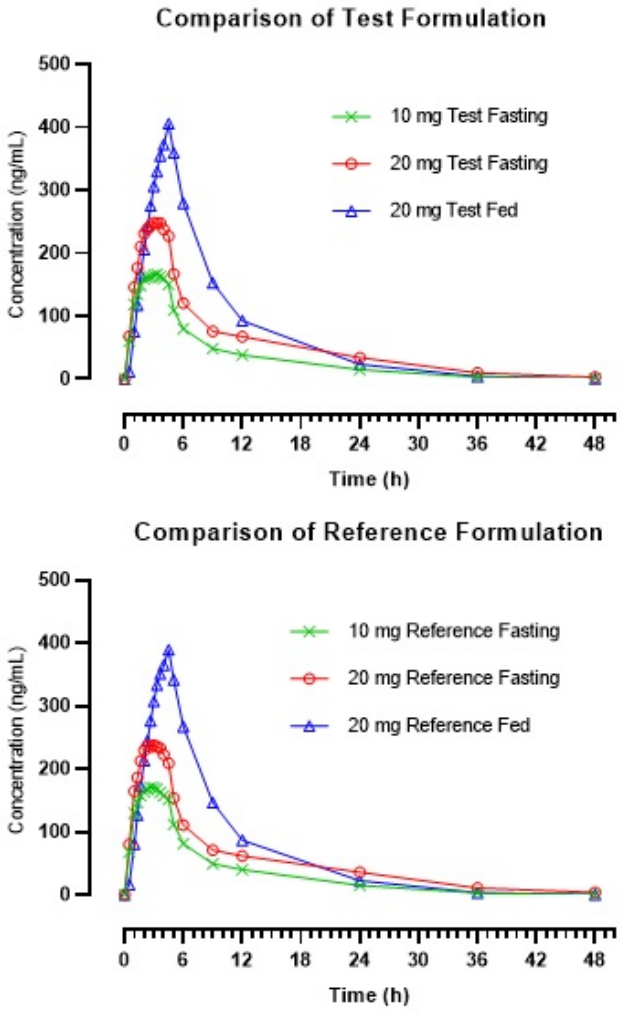
Table 6: Bioequivalence for the 10 mg and 20 mg Fasting condition and 20 mg Fed Condition.

Under fasting conditions, pharmacokinetic parameters Cmax and AUC of 10 mg and 20 mg rivaroxaban increased with dose but were less than dose proportional. This result meets that found in literature [14].

The 20 mg studies showed that the main PK parameters as Tmax, Cmax, AUC0-t, AUC0-inf of the test, and the reference tablets presented similar performances both in the fasting and fed, individually, as well described in the literature [14, 19, 20].

Accordingly the prescribing information of reference drug 21, oral absorption of rivaroxaban is nearly complete and oral bioavailability is high (80-100%) for the 10 mg dose, regardless of fasting/feeding conditions. Intake with food does not affect the AUC or Cmax of rivaroxaban at the 10 mg dose. Based on literature and prescribing information, rivaroxaban 10 mg tablet can be taken with or without food, what meet the literature and because that was assessed only in fast state [3, 5, 20].

Due to the reduced degree of absorption, an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken with food, increases in mean AUC of around 39% were observed when compared to ingestion under fasting conditions, indicating almost complete absorption and high oral bioavailability. Thus, rivaroxaban 15 mg and 20 mg should be taken with food, reaching the desired therapeutic levels, as indicated in the prescribing information, and as demonstrated in the previous pharmacokinetics studies [5, 9, 14, 20, 21] . The current studies showed the same pattern, reiterating the posology of different presentations, and justifying the designs. Comparison of 10 mg fast, 20 mg fasting and fed are shown in the Figure 4, separated by Test and Reference formulations.



Figures 4a: (central figure) and 4b. Mean plasma concentrations of Rivaroxaban, Test (T) and Reference (R) formulations 10mg, 20 mg

Conclusion

In the statistical analysis of Rivaroxaban on data of 42 evaluable subjects (under fasting condition) and 44 subjects (under fed conditions), it was observed that, the 90% confidence interval of primary variables was within the acceptance ranges 80.00%-125.00% and the upper limit of 90% CI of the SWT/SWR ratio of primary variables was ≤ 2.5. The sample size selected for bioequivalence study was adequate once power in the study was more than 80%. Thus, it has been concluded that the Eurofarma products are bioequivalent with the reference products under fasting and fed conditions.

Both products were considered well tolerated by the participants according to adverse events and their severities, clinical examination, electrocardiogram, and laboratorial assays, The profile of the adverse events matches the literature and the package insert of the reference product.

The use of generic drugs in the clinical practice must be encouraged and be an alternative for public health systems to reduce costs and keeping the quality of the treatment offered, once bioequivalence trials show interchangeability between generic and reference drugs.

Based on statistical results, it can be concluded that Rivaroxaban manufactured by Eurofarma Laboratórios S/A tested in these studies, complies with regulatory requirements to be considered bioequivalent to the reference drug and according to the above,

the Eurofarma product can be interchangeable with the Xarelto®, Bayer, based on their biopharmaceutical performance. Both products were well tolerated and can be considered equally effective, safe and interchangeable in medical practice based on their pharmacokinetic effect. The test product is bioequivalent and can be interchangeable with the reference product and would be beneficial to patients with additional availability of the drug at a lower cost.

Acknowledgments

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