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Pharmacodynamic Study of Parallel Groups Comparing the Effect of Rivaroxaban 20 Mg (Laboratorios Leti, S.A.V.) vs Rivaroxaban 20 Mg (Bayer Laboratories) on Prothrombin Time

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Abstract

Background: The prevalence of both atrial fibrillation (FA) and diabetes mellitus (DM) is increasing and they often occur together and constitute a high risk of thrombosis. Rivaroxaban is a Factor Xa inhibitor with a rapid onset and disappearance of action after oral administration; it acts by inhibiting the active form of the coagulation factor. In order to reflect the effect of the action of Rivaroxaban, we used the prothrombin time (PT); however, it´s not the most accurate, but it is the one available in our community. **Methods:** This was a prospective, randomized, analyst-blinded, parallel group clinical study to verify the efficacy of Rivaroxaban Leti 20 mg (RL) (12 volunteers vs Rivaroxaban Bayer 20 mg (RB) (13 volunteers). The variables were determination of PT and Partial Thromboplastin Time (aPTT) at baseline and at 24, 48 and 72 hours after administering a daily dose of 20 mg for three days. The determination was carried out with the IDG method (Integrated Diagnostics Group Sanzay Corporation) with an International Sensitivity Index (ISI) of 1.17 PT and aPTT were taken before the first dose, and then, every day during the next 3 days, three hours after the ingestion of their daily dose at 7 am. **Results:** The 25 healthy volunteers were similar in age, BMI, and SBP/DBP level with a greater number of men in the Bayer group. The efficacy of rivaroxaban was similar in both groups with prolongation of PTT to the 2nd day of treatment with PT, and percentage changes from baseline (14.46 ± 0.97 for RB vs 14.17 ± 0.94 RL p: 0.45), PTT results and percentage changes from the base (RB: 34 ± 4.53 RL: 33.46 ± 2.82). The safety of rivaroxaban was good in both groups with no serious adverse events. The equivalence in the logarithmically transformed PT result (ln) on day two, Mean and CI (90%) 99.2 (94.4 - 104) and 100 (99.5 - 100.8); neither the means nor the 90% confidence in-

tervals of the PT variable transformed logarithmically to ensure its normality, were far from the 80% - 125% allowed for declaration of similarity. **Conclusion:** The test formulation Rivaroxaban Asarap® 20 mg, manufactured by Leti Laboratories, is interchangeable or bioequivalent in clinical and laboratory response to the reference formulation Xarelto® manufactured by Bayer Laboratories.

Keywords

Pharmacodynamic Study, Rivaroxaban, Clinical Trial, PT, aPTT

1. Introduction

Coagulation is the result of a coordinated interaction of blood proteins, circulating cells, vasculature cells, and extracellular matrix proteins in the vessel wall This complex mechanism makes its evaluation difficult in the laboratory, which is only limited to measuring circulating coagulation proteins and circulating cells, while vascular elements are not measurable.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the tests generally used as screening to evaluate most coagulation factors. The PTTa evaluates the factors involved in the intrinsic coagulation pathway while the PT evaluates the extrinsic pathway; both agree on the factors of the common path.

To perform the PT and aPTT test, both require blood anticoagulated with sodium citrate, which works as a calcium chelator. It is very important to take into account that, if the amount of anticoagulant is inappropriate or the time elapsed between blood collection and testing is more than 4 hours, some labile factors such as factors V and VII are inactivated [1].

Prothrombin time activates coagulation when tissue factor or thromboplastin and calcium are added; the normal result ranges from 10 to 14 seconds with >60% activity. Depending on the type of thromboplastin added, the result can vary widely, which is why a standardized method has been developed to express these variations: international normalized ratio (INR).

For the aPTT test, phospholipids, calcium and a contact factor initiator such as kaolin or silica are added to the citrated plasma. The normal result ranges from 25 to 45 seconds; however, it is important to know the reference values of each laboratory [1].

Rivaroxaban (bay 59-7939) is an oral anticoagulant developed and marketed by Bayer, which acts by inhibiting the active form of coagulation factor X (factor Xa).

One way to reflect the effect of Rivaroxaban concentration is the prothrombin time, but important differences in responsiveness have been observed between thromboplastins.

Based on this, the international sensitivity index (ISI) was created, which reflects the responsiveness of each thromboplastin reagent for the reduction of vi-

tamin K-dependent coagulation factors. The recombinant tissue factor is assigned an ISI of 1.0. It is important to remember that the ISI reflects sensitivity to the effect of warfarin on PT and may not reflect the activities of factors influenced by other drugs or medical conditions [1] [2] [3].

It was debated whether the ISI established for monitoring anticoagulation with warfarin was valid for Rivaroxaban, or other Xa inhibitors, because the drug-induced effect has been shown to increase the variability between thromboplastins.

However, a study was carried out to normalize the results, with different thromboplastin reagents, which could pave the way to the establishment of universal therapeutic intervals for Rivaroxaban with selected patients.

The results of this study are consistent with the hypothesis that the ISI/INR calibration model, once used for vKa and then applied to liver disease and disseminated intravascular coagulation, is also feasible for Rivaroxaban and possibly other new direct inhibitors of fXA [3].

It is recommended to use thromboplastins whose ISI is not higher than 1.4 [4] [5].

In this study the laboratory used a reagent with an ISI of 1.17, which given the conditions of the country, was the lowest index available.

The oral bioavailability of Rivaroxaban is 80% - 100% for the 10 mg dose, regardless of food intake. Under fasting conditions, Rivaroxaban 10 mg, 15 mg and 20 mg show dose-proportional bioavailability. In a fasted state, the pharmacokinetics of Rivaroxaban is approximately linear up to approximately 15 mg once daily, and bioavailability is reduced to 66% after a 20 mg tablet; at higher doses, bioavailability decreases as a result of solubility. Food does not affect the area under the concentration-time curve or the maximum plasma concentration (Cmax) of the 10 mg dose. When the oral dose of Rivaroxaban is administered, it is absorbed rapidly, with Cmax occurring 2 - 4 hours after ingestion of the tablets [6]-[13].

At total daily oral doses of Rivaroxaban of 5 - 60 mg, Cmax ranges (mean values) from 40 μg/l to 400 μg/l and the minimum plasma concentration (Ctrough) (mean values) is 8 μg/l to 160 μg/l [10].

No relevant accumulation occurs beyond steady state in healthy individuals [6]. The elimination of Rivaroxaban from plasma occurs with a terminal half-life of 5 - 9 hours in young individuals [8] [12] and 11 - 13 hours in the elderly [14]. Rivaroxaban has a dual mode of elimination [15].

Of the administered dose, approximately two-thirds undergo metabolic degradation, half of which is eliminated through the kidneys and the other half via the hepatobiliary route. The last third of the administered dose undergoes direct renal excretion [16] [17].

In our country, we need to demonstrate the similarity between second brands of an active ingredient, comparing them with the innovative product, in our case the rivaroxaban from Leti Laboratories, was compared with rivaroxaban from

Bayer Laboratories, Xarelto.

2. Objective

To verify, under a parallel design, the pharmacodynamic equivalence of Rivaroxaban from Leti Laboratories: (RL) 20 mg tablets in three days, one dose/day, test product, compared to the Rivaroxaban product from Bayer Laboratories, reference product, Xarelto® (RB) of 20 mg in three doses, one dose/day, in a population of healthy volunteers.

3. Materials and Methods

This was a randomized, analyst-blinded, parallel-group clinical study, and was carried out at the Uslar Medical Center in Venezuela during 2023.

We included healthy volunteers, aged between 18 to 45 years; their good health was confirmed by complete medical examination (clinical history, physical examination, personal history) and paraclinical tests (laboratory routine: complete hematology, urea, creatinine, glycemia, cholesterol, triglycerides, PT, aPTT, liver biochemistry, HIV by the Elisa method, serology for hepatitis B and C, urine and feces, ECG and chest x-ray).

People were summoned by public notice. Those who attended the notice received a pre-selection form, and an information form about the study. If they were interested in participating in it, they received the subjects' informed consent and once signed, the volunteer entered the study.

We excluded from the study subjects with the following findings:

Quetelet index less than 18 or greater than 30. Volunteers with a history of nephropathies, liver diseases (including viral processes), hematological disorders, gastritis, gastric ulcer, rectocolitis, allergy to similar medications, coagulation disorders, cardiovascular diseases, central nervous system (CNS), metabolic diseases or any condition that may interfere with the absorption, metabolism and/or excretion of the drug. Active infections, whether viral, bacterial of any type, or fungal. Subjects under any therapeutic regimen or who have been under any therapeutic regimen during the 30 days prior to the study, including oral contraceptives (depending on the medication used, the period may be reduced to 15 days), always subject to the discretion of the study coordinating doctor.

Subjects with a history of alcohol abuse, drug abuse, smoker of more than 10 cigarettes a day. Blood donor in the last 3 months. Subjects who participated in a similar study in the last 3 months. Allergy to the study drug. Pregnancy (positive pregnancy test) and/or breastfeeding period. Obvious mental illnesses or behavioral disorders that may interfere with research.

At the beginning, the volunteers underwent interrogation and clinical examination in order to guarantee their status as healthy volunteers. On the first day, 6 cc of blood were drawn to determine baseline PT and aPTT. This determination was performed with the IDG Integrated Diagnostics Group Sanzay Corporation method, with an ISI of 1.17 with the the coagulometric method.

Subjects were randomly assigned to one of two groups: Rivaroxaban Leti (RL) 20 mg vs Rivaroxaban 20 mg from Bayer Laboratories (RB).

Each subject was given a box with four tablets of the study product that he should take that day and for the next two days (1 window tablet).

Drug under study, chemical name: 5-cloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3 oxazolidin-5 il}metil)-2-tiofeno-carboxamida; Generic name: Rivaroxaban; tradename Asarap®, pharmaceutical form tablets, manufacturer laboratory, Leti Laboratories, S.A.V. Venezuela, dose 20 mg.

On the first day and the following two days, the subject had to take the tablet at 7 am and undergo the PT and aPTT test, for which 6 cc of blood was withdrawn for the determination, 3 hours after taking the tablet, or be at 10 am.

The size of the sample was calculated taking into consideration the PT data obtained from the results of a healthy population in a previous study: Standardization of quality control in the haemostasis laboratory Olga Silvia Pantaleón Bernal, María Eugenia Triana Mantilla, Cs Milagros Tomasa García Mesa La Habana Cuba, Instituto Nacional de Angiología y Cirugía Vascular, NACV. In that study, average PT was 13.1 seconds with a standard deviation of 0.94. Using this data gives us a power greater than 90% to detect a difference of 2 points in PT with an Alpha error of 0.05, with 12 subjects in each group.

The variables: age, height, BMI, SBP, DBP, and pulse were evaluated using Student's t-test, paired within group and unpaired between groups. The variable sex was evaluated using Chi^2.

The variables: PT and PTT were evaluated using the Wilcoxon Rank Test within group and Mann Whitney U between groups.

4. Results

Thirty-nine volunteer subjects applied, of which 14 were removed due to alterations in laboratory examinations. They were referred to different specialists to address these alterations.

There were no differences between the groups in relation to age, sex, weight, body mass index, blood pressure or pulse, these variables remained unchanged during the study and at the final examination, 15 days after the end of the study.

There were no differences between the anthropometrical variables and the background between both groups (Table 1).

In both groups, there was a prolongation of prothrombin time (PT). When the comparative analysis of the data transformed into logarithms in base e, was carried out to ensure their normality, we did not find any differences between the groups in the prolongation of PT (Table 2).

In both groups, there was a prolongation of activated partial thromboplastin time (aPTT). When the comparative analysis of the data transformed into logarithms in base e, was carried out to ensure their normality, we did not find any differences between the groups in the prolongation of aPTT (Table 3).

When we carried out the relationships of the PT logarithmically transformed

Table 1. Description of the evaluated population.

Parameter	Rivaroxaban Bayer	Rivaroxaban Leti	p
Age	31.8 ± 9.3	32.0 ± 9.6	0.95
M/F Sex	11/2	6/6	0.58
Weight	71.2 ± 13.3	75.3 ± 13.3	0.46
Size	1.69 ± 0.1	1.72 ± 0.1	0.51
BMI	24.83 ± 3.9	25.6 ± 4.7	0.66
PAS	113.9 ± 10.4	115.4 ± 9.2	0.69
PAD	69.2 ± 6.7	67.8 ± 6.6	0.58
Pulse	66.0 ± 9.6	70.4 ± 7.6	0.21
Family history	Arterial Hypertension N = 4 Diabetes N = 2 Osteoporosis = 1 Alcoholic Liver Cirrhosis = 1	Arterial Hypertension N = 4 Diabetes N = 1. Renal Lithiasis N = 1 Thalassemia N = 1 Prostate Cancer N = 1. Breast Cancer N = 1	

Table 2. PT results, and percentage changes in the base.

	Rivaroxaban Bayer					Rivaroxaban Leti			
n°	Start	Day 1	Day 2	Day 3	N°	Start	Day 1	Day 2	Day 3
1	13	13	16	15	2	14	14	15	15
4	13	15	13	14	3	14	14	15	16
6	14	14	14	15	5	14	14	15	15
8	12	13	15	16	7	13	14	14	15
10	14	14	14	14	9	14	14	15	15
12	13	14	14	14	13	15	14	15	14
14	14	14	15	15	16	13	13	13	14
15	15	16	16	16	18	14	14	14	14
17	14	13	14	13	20	14	15	14	13
19	15	13	15	14	22	13	14	12	12
21	14	13	14	13	23	14	14	14	14
24	14	13	13	13	25	15	15	14	14
26	14	16	15	13					
Average	13.77	13.92	14.46	14.23		13.92	14.08	14.17	14.25
SD	0.83	1.12	0.97	1.09		0.67	0.51	0.94	1.06
	p between groups					063	065	045	096
% Change from base		1.12	5.03	3.35			1.20	1.80	2.40

Table 3. aPTT results and percentage changes in the base.

Rivaroxaban Bayer					Rivaroxaban Leti				
N°	Start	Day 1	Day 2	Day 3	N°	Start	Day 1	Day 2	Day 3
1	30	34	28	32	2	31	28	32	34
4	34	32	37	38	3	28	34	37	32
6	34	38	37	39	5	36	35	35	34
8	34	31	36	40	7	34	34	37	35
10	40	34	31	31	9	32	35	36	34
12	32	32	34	31	13	32	41	38	38
14	30	32	32	32	16	28	28	28	25
15	36	40	35	38	18	40	41	36	42
17	34	39	31	34	20	31	31	29	28
19	42	34	36	37	22	32	30	27	28
21	34	39	32	35	23	39	32	36	44
24	26	31	31	32	25	36	39	34	35
26	27	34	35	31					
average	33.31	34.62	33,46	34,62		33.25	34.00	33.75	34.08
SD	4.53	3.25	2.82	3.38		3.86	4.53	3.82	5.55
p between groups						**0.97**	**0.70**	**0.83**	**0.77**
% Change from base		3.93	0.46	3.93			2.26	1.50	2.50

Table 4. Equivalence in the result of logarithmically transformed PT (Ln).

	Start	Day 1	Day 2	Day 3
Average %	100.4	100.5	99.2	100.1
Minimum %	95.5	95.6	94.4	95.1
Maximum %	105.4	105.4	104.1	105.0

Table 5. Equivalence in the logarithmically transformed aPTT Result (Ln).

	Start	Day 1	Day 2	Day 3
Average %	100.0	99.4	100.2	99.3
Minimum %	99.4	98.7	99.5	98.5
Maximum %	100.6	100.1	100.8	100.2

means, as well as the 90% confidence intervals, we found that neither the means, nor the minimum and maximum values, were outside the 80% - 125% range required for Declaration of Similarity, at any time (Table 4).

When we carried out the relationships of the aPTT logarithmically trans-

formed means, as well as the 90% confidence intervals, we found that neither the means, nor the minimum and maximum values, were outside the 80% - 125% range required for Declaration of Similarity, at any time (**Table 5**).

5. Discussion

In the Factor CKET-AF study, Rivaroxaban was not inferior to warfarin for the prevention of stroke and systemic embolism [2] in the "intention to treat" analysis, while in the "per protocol" analysis it achieved statistical superiority with a reduction in 21% rate of stroke or embolism versus warfarin.

Rivaroxaban is a potent and selective inhibitor of factor Xa. It is absorbed orally and its bioavailability is greater than 80%. Its effect is to prolong the prothrombin time and the activated partial thromboplastin time. Its pharmacodynamic equivalence was carried out to compare action on prothrombin time in healthy volunteers [3] based on changes in laboratory parameters, PT and PTT in healthy volunteers.

The Bioequivalence studies carried out in healthy volunteers with a dose of 10 mg y 20 mg, in a 4-period, randomized, open-label and crossover study in healthy subjects under fasting or fed conditions, indicated that the 2 different formulations of rivaroxaban compared were bioequivalent [18] [19].

On this occasion, it has been decided to compare two formulations of rivaroxaban evaluating its action on the coagulation parameters. The two groups of volunteers were similar at the beginning of the study in terms of age, sex, weight, height, SBP, DBP, pulse and history (**Table 1**).

In both groups, there was a prolongation of PT and aPTT, without reaching a difference between groups and their response (**Table 2** and **Table 3**).

When the relationship between the PT and aPTT, logo-transformed variables, were analyzed, it was found that neither the means nor the confidence intervals of both variables are far from the 80% to 125% interval. The test formulation Rivaroxaban Leti 20 mg, manufactured by Leti Laboratories (Asarap®) is interchangeable or equivalent in clinical and laboratory response to the reference formulation Xarelto®, manufactured by Bayer (**Table 4** and **Table 5**).

A bioequivalence study was carried out with this same product Rivaroxaban from Laboratorios Leti, to demonstrate the bioequivalence (BE) and safety of a generic formulation of rivaroxaban by comparing their pharmacokinetic (PK) parameters through statistical data and criteria of validation. Oral tablet formulations of 20 mg of a commercial product rivaroxaban reference (R) were tested against a generic of Leti Laboratories product test (T) in 24 healthy adults under fasting condition. The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, and crossover study. Blood samples were collected pre-dose and at specified intervals up to 48-h post-dose to evaluate PK parameters by quantifying the concentration of rivaroxaban in plasma using a validated Liquid chromatography-mass spectrometry (LC-MS/MS) method of analysis. Statistics and confidence intervals (CIs) were

calculated for BE purposes. Results: The geometric means of the T/R ratios and 90% confidence intervals (CIs) were: Cmax 87.80% (82.74% - 93.12%), AUC0-t 85.96% (81.88% - 90.24%), and AUC0-∞ 86.13% (82.2% - 90.35%). All PK parameters are within BE acceptance range of 80% - 125% for demonstration of average bioequivalence [20].

According to these studies, rivaroxaban, from Leti Laboratories in Venezuela, has been shown by biequivalence and pharmacodynamic equivalence, to be similar to the international reference product.

6. Study Limitations

The absolute bioavailability of rivaroxaban, at higher doses, rivaroxaban shows decreased absorption, with a dose-dependent reduction in bioavailability and absorption rate. This effect is more marked on an empty stomach than after eating, when using the 20 mg presentation we could have reductions in the bioavailability of rivaroxaban that could affect the PT and PTTa results.

On the other hand, although it is recommended that a reagent be used to determine PT with an ISI value of less than 1.4, ideally it should be closer to 1.0. In this study, a reagent with an ISI of 1.17 was used, which gave the conditions of the country, was the lowest index available.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] López-Santiago, N. (2016) Pruebas De Coagulación. *Acta Pediátrica De México*, **37**, 241-245. https://doi.org/10.18233/APM37No4pp241-245

[2] Konkle, B.A. (2016) Direct Oral Anticoagulants Monitoring Anticoagulant Effect. *Hematology/Oncology Clinics of North America*, **30**, 995-1006. https://doi.org/10.1016/j.hoc.2016.05.004

[3] Tripodi, A., Chantarangkul, V., Guinet, C. and Samama, M.M. (2011) The International Normalized Ratio Calibrated for Rivaroxaban Has the Potential to Normalize Prothrombin Time Results for Rivaroxaban-Treated Patients Results of an *in Vitro* Study. *Journal of Thrombosis and Haemostasis*, **9**, 226-228. https://doi.org/10.1111/j.1538-7836.2010.04106.x

[4] WHO/BS/2016.2294 Calibration of the Proposed 5th IS for Thromboplastin, Human, Recombinant, Plain (rTF/16; Study Code 14/001) and the Proposed 5th IS for Thromboplastin, Rabbit, Plain (RBT/16; study code 15/001).

[5] Retamales Castelletto, E. and Moscoso Espinoza, H. (2021) Recomendaciones para la etapa pre-analítica, analítica y post-analítica en las pruebas de coagulación. Departamento Laboratorio Biomédico Nacional y de Referencia. Instituto de Salud Pública de Chile.

[6] Perzborn, E., Roehrig, S., Straub, A., Kubitza, D. and Misselwitz, F. (2011) The Discovery and Development of Rivaroxaban, an Oral, Direct Factor Xa Inhibitor. *Nature Reviews Drug Discovery*, **10**, 61-75. https://doi.org/10.1038/nrd3185

[7] Xarelto, INN-rivaroxaban. Summary of Product Characteristics 2013. https://ec.europa.eu/health/documents/community-register/2013/20130805126532/anx_126532_en.pdf

[8] Kreutz, R. (2012) Pharmacodynamic and Pharmacokinetic Basics of Rivaroxaban. *Fundamental & Clinical Pharmacology*, **26**, 27-32. https://doi.org/10.1111/j.1472-8206.2011.00981.x

[9] Mueck, W., Stampfuss, J., Kubitza, D. and Becka, M. (2014) Clinical Pharmacokinetic and Pharmacodynamic Profile of Rivaroxaban. *Clinical Pharmacokinetics*, **53**, 1-16. https://doi.org/10.1007/s40262-013-0100-7

[10] Samama, M.M., Contant, G., Spiro, T.E., Perzborn, E., Le Flem, L., Guinet, C., Gourmelin, Y., Rohde, G. and Martinoli, J.L. (2013) Laboratory Assessment of Rivaroxaban: A Review. *Thrombosis Journal*, **11**, Article No. 11. https://doi.org/10.1186/1477-9560-11-11

[11] Kubitza, D., Becka, M., Voith, B., Zuehlsdorf, M. and Wensing, G. (2005) Safety, Pharmacodynamics, and Pharmacokinetics of Single Doses of Bay 59-7939, an Oral, Direct Factor Xa Inhibitor. *Clinical Pharmacology & Therapeutics*, **78**, 412-421. https://doi.org/10.1016/j.clpt.2005.06.011

[12] Mueck, W., Lensing, A.W., Agnelli, G., Decousus, H., Prandoni, P. and Misselwitz, F. (2011) Rivaroxaban: Population Pharmacokinetic Analyses in Patients Treated for Acute Deep-Vein Thrombosis and Exposure Simulations in Patients with Atrial Fibrillation Treated for Stroke Prevention. *Clinical Pharmacokinetics*, **50**, 675-686. https://doi.org/10.2165/11595320-000000000-00000

[13] Mueck, W., Eriksson, B.I., Bauer, K.A., Borris, L., Dahl, O.E., Fisher, W.D., Gent, M., Haas, S., Huisman, M.V., Kakkar, A.K., Kalebo, P., Kwong, L.M., Misselwitz, F. and Turpie, A.G. (2008) Population Pharmacokinetics and Pharmacodynamics of Rivaroxaban—An Oral, Direct Factor Xa Inhibitor—In Patients Undergoing Major Orthopaedic Surgery. *Clinical Pharmacokinetics*, **47**, 203-216. https://doi.org/10.2165/00003088-200847030-00006

[14] Kubitza, D., Becka, M., Wensing, G., Voith, B. and Zuehlsdorf, M. (2005) Safety, Pharmacodynamics, and Pharmacokinetics Of Bay 59-7939—An Oral, Direct Factor Xa Inhibitor—After Multiple Dosing in Healthy Male Subjects. *European Journal of Clinical Pharmacology*, **61**, 873-880. https://doi.org/10.1007/s00228-005-0043-5

[15] Kubitza, D., Becka, M., Roth, A. and Mueck, W. (2008) Dose-Escalation Study of the Pharmacokinetics and Pharmacodynamics of Rivaroxaban in Healthy Elderly Subjects. *Current Medical Research and Opinion*, **24**, 2757-2765. https://doi.org/10.1185/03007990802361499

[16] Weinz, C., Schwarz, T., Kubitza, D., Mueck, W. and Lang, D. (2009) Metabolism and Excretion of Rivaroxaban, an Oral, Direct Factor Xa Inhibitor, in Rats, Dogs and Humans. *Drug Metabolism & Disposition*, **37**, 1056-1064. https://doi.org/10.1124/dmd.108.025569

[17] Mueck, W., Schwers, S. and Stampfuss, J. (2013) Rivaroxaban and Other Novel Oral Anticoagulants: Pharmacokinetics in Healthy Subjects, Specific Patient Populations and Relevance of Coagulation Monitoring. *Thrombosis Journal*, **11**, Article No. 10. https://doi.org/10.1186/1477-9560-11-10

[18] Ding, S.J., Wang, L., Xie, L.J., Zhou, S.F., Chen, J., Zhao, Y.Q., Deng, W.J., Liu, Y., Zhang, H.W. and Shao, F. (2020) Bioequivalence Study of 2 Formulations of Rivaroxaban, a Narrow-Therapeutic-Index Drug, in Healthy Chinese Subjects Under Fasting and Fed Conditions. *Clinical Pharmacology in Drug Development*, **9**, 346-352. https://doi.org/10.1002/cpdd.742

[19] Genis-Najera, L., Sañudo-Maury, M.E. and Moquete, T. (2022) A Single-Blind, Randomized, Single-Dose, Two-Sequence, Two-Period, Crossover Study to Assess the Bioequivalence between Two Oral Tablet Formulations of Rivaroxaban 20 mg in Healthy Mexican Volunteers. *Clinical Pharmacology in Drug Development*, **11**, 826-831. https://doi.org/10.1002/cpdd.1092

[20] Pena, E., Inatti, A. and Martin, X.S. (2023) Bioequivalence Study of Two Formulations of Rivaroxaban in Healthy Adult Subjects under Fasting Conditions. *American Journal of Pharmacotherapy and Pharmaceutical Sciences*, **2**, Article No. 8. https://doi.org/10.25259/AJPPS_2023_008