Bioequivalence of two different formulations of rivaroxaban film-coated tablet

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Aims: Studies aimed to evaluate the bioequivalence of 10 mg and 20 mg of Rivaroxaban film-coated tablets developed by Gedeon Richter Plc. (Hungary) compared to the reference product Xarelto® (Bayer AG, Germany).
Methods: Two randomized, open-label, two-period, two-sequence crossover studies were conducted in healthy male subjects. Study A assessed the 10 mg dose under fasting conditions (n=42), while Study B evaluated the 20 mg dose under fed conditions (n=30). Pharmacokinetic parameters including AUC_{inf}, AUC_{inf}, and C_{max} were determined using validated LC-MS/MS methods. Bioequivalence was concluded if the 90% confidence intervals (CIs) for the test/reference ratios of these parameters fell within the 80.00–125.00% range.
Results: In Study A, the geometric mean ratios (GMRs) for AUC_t and C_{max} were 97.32% and 90.39%. In Study B, the GMRs for AUC_t and C_{max} were 98.35% and 95.98%. All 90% CIs were within the predefined bioequivalence limits. Both formulations were well tolerated. Only mild and well-known treatment-emergent adverse events (TEAEs) were reported,-without any-treatment discontinuation.
Conclusions: The 10 mg and 20 mg Rivaroxaban formulations developed by Gedeon Richter Plc. are bioequivalent to Xarelto® and are safe and well tolerated. These results support their use as clinically interchangeable alternatives to the reference product.

Keywords: Rivaroxaban, bioequivalence, stroke, systemic embolism, venous thromboembolism
Conflict of Interests: The authors declare no conflict of interest

1. Introduction

The direct oral anticoagulant (DOAC) - like apixaban, dabigatran, edoxaban, and rivaroxaban- have all shown at least non-inferior efficacy compared with warfarin for the prevention of thromboembolism, with one notable benefit of a 50% reduction in intracranial haemorrhage [1].

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi [2].

Rivaroxaban is a DOAC extensively used in clinical practice for the prevention and treatment of thromboembolic disorders. According to the European Society of Cardiology (ESC) guidelines, rivaroxaban is particularly recommended for patients with non-valvular atrial fibrillation to prevent stroke and systemic embolism.

Rivaroxaban is preferred over traditional vitamin K antagonists (VKAs) due to its ease of use, predictable pharmacokinetics, reduced need for monitoring and has a favorable safety profile [1,3,4].

Rivaroxaban is rapidly absorbed with maximum plasma concentrations (C_{max}) appearing 2–4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete, and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with

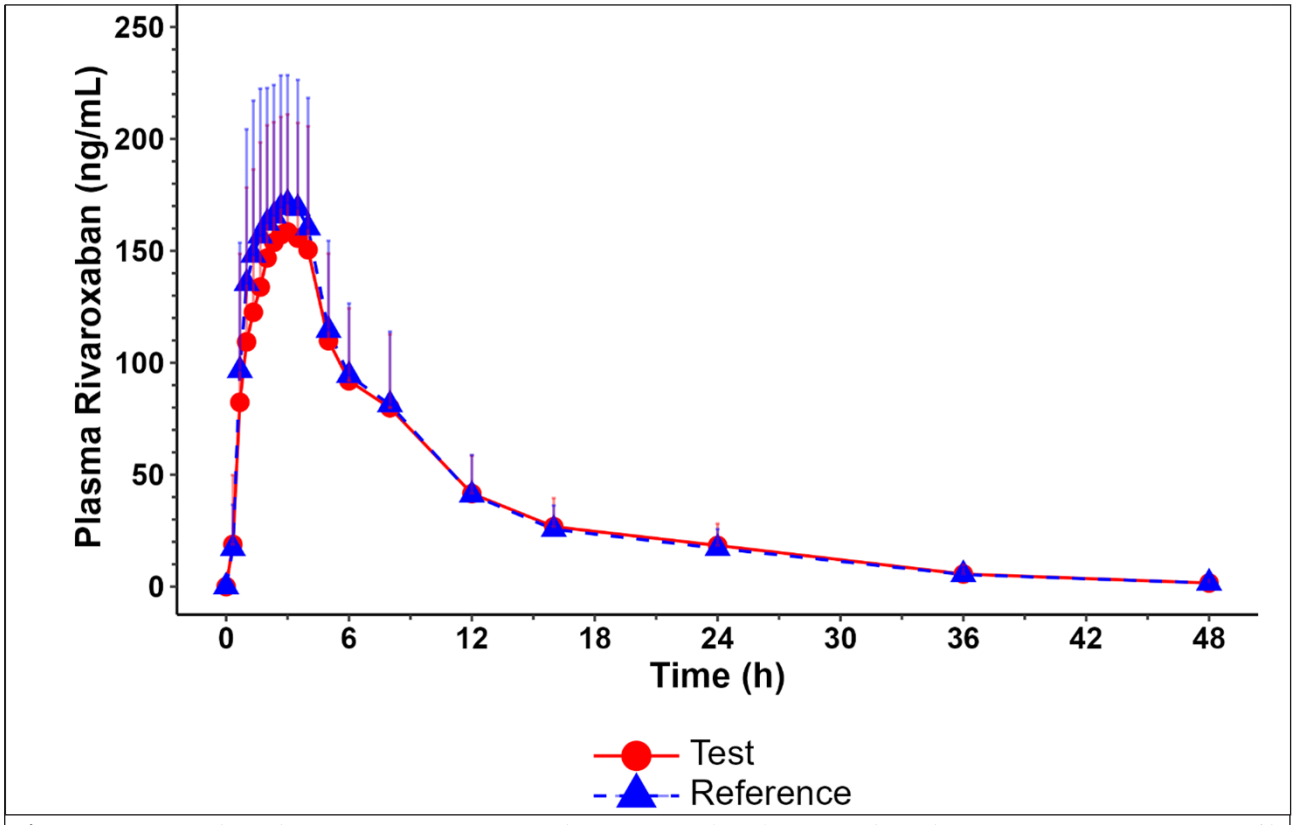

Figure 1. *Rivaroxaban plasma concentration in study A – Mean (+SD) Rivaroxaban plasma concentration - time profile (linear scale) following single oral administration of Rivaroxaban 10 mg tablet (Test) and Xarelto® 10 mg tablet (Reference) in Study A*

half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of five to nine hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly [2].

The primary objective of our bioequivalence (BE) study was to evaluate the relative bioavailability of Rivaroxaban 10 mg (study A)/ 20 mg (study B) film-coated tablets (Gedeon Richter Plc., Hungary, brand name: Kardatuxan or Riqulatron or Rivaroxaban Richter) and Xarelto® 10 mg (study A) /20 mg (study B) film-coated tablets (Bayer AG, Germany) after a single dose in healthy male subjects under fasted (study A) and fed (study B) conditions. The secondary objective of this study was to evaluate the safety and tolerability of the study treatments. Both studies were conducted according to European Medicines Agency (EMA) guidelines [5,6].

2. Materials and Methods

2.1 Study Design

Both studies were randomized, open-label, two-period, two-treatment, two-sequence, crossover BE study conducted to evaluate the pharmacokinetics and bioequivalence of Rivaroxaban 10 mg (Study A) and 20 mg (Study B) film-coated tablets from Gedeon Richter Plc., Hungary (test formulation) compared to the reference formulation Xarelto® 10 mg and 20 mg film-coated tablets from Bayer AG, Germany, respectively. Fed conditions were necessary in case of study B, as Rivaroxaban at higher doses displays dissolution limited absorption with decreased bioavailability of 40% and decreased absorption rate [2]. The 10 mg doses were administered under fasting conditions.

Studies were performed in compliance with the most current International Council for Harmonisation Good Clinical Practice (ICH-GCP) [7], Declaration of Helsinki [8] and EMA product specific guideline [6], including, but not limited to, the associated Integrated Addendum and described Quality Management System therein, which en-

Table I. *Pharmacokinetic parameters of Test and reference products*

	Study A (10 mg)		Study B (20 mg)	
	Rivaroxaban (test)	Xarelto® (reference)	Rivaroxaban (test)	Xarelto® (reference)
AUC_t (hr*ng/mL)	1593.88 (530.47)	1643.20 (519.44)	3037.17 (857.25)	3110.10 (965.45)
AUC_{inf} (hr*ng/mL)	1625.35 (535.53)	1675.32 (528.12)	3081.90 (869.16)	3148.44 (973.94)
C_{max} (ng/mL)	179.87 (53.47)	198.05 (57.26)	352.87 (77.38)	372.00 (100.18)

Arithmetic mean (SD) of the pharmacokinetic parameters of Rivaroxaban (test) and Xarelto® (reference) after single oral dose in Study A (n=42) and Study B (n=30)

compasses a Quality Risk Management process that manages quality throughout all stages of the clinical trial process and archiving of essential documents.

2.2 Participants

According to the Summary of Product Characteristics (SmPC) of the originator Xarelto® [2], it was not obligatory but recommended to conduct the BE studies with the inclusion of healthy male volunteers only, as pregnancy and breast-feeding is contraindicated due to the potential reproductive toxicity, the intrinsic risk of bleeding, and the evidence that rivaroxaban passes the placenta and data from animal studies indicate that rivaroxaban is secreted into the milk. Therefore, healthy, non-smoking, adult male participants 18 years of age or older, with a body mass index (BMI) of 18.5-30.0 kg/m², were enrolled in the studies.

Key inclusion criteria included no history of clinically significant cardiovascular, hepatic, or renal disease, as well as no contraindications for rivaroxaban. Participants were excluded if they had any history of hypersensitivity to rivaroxaban or any other component of the formulations. All participants provided written informed consent before participating in the study.

Assuming 25% intra-subject variability (CV_{intra}) for fasting (study A) and 25% CV_{intra} for fed (study B) and a difference between the treatment means of 5% or less, the necessary sample size for a 90% probability of the 90% confidence intervals (CIs) of the treatment means ratio to be within the 80.00 to 125.00% range was estimated to be 38 (for study A) and 26 (for study B) subjects. Similarly, four extra subjects were included in both studies to account for potential dropouts, resulting in a total of 42 and 30 subjects enrolled in the studies respectively.

2.3 Treatments and Pharmacokinetic Sampling

The studies consisted of a 4-week screening period, during which the volunteers were assessed if they fulfilled all inclusion criteria and none of the exclusion criteria. Eligible subjects were then confined from 10 h before study drug administration (Day one and Day 12) until 24 h post dose (last pharmacokinetic (PK) sampling).

The participants were randomly assigned to one of the two possible sequences in both studies: TR or RT, where the test formulation (T) was the rivaroxaban 10 mg or 20 mg tablet developed and manufactured by Gedeon Richter Plc., and the reference formulation (R) was Xarelto® 10 mg or 20 mg film-coated tablets from Bayer AG, respectively. Participants received a single dose of either the test or reference formulation administered as a 10 mg or 20 mg oral tablet, under fasting conditions for Study A (10 mg dose) and under fed conditions ensured with a high-fat, high-calorie breakfast in case of Study B (20 mg dose).

Consistently for both studies the treatments were administered in two periods, with a washout period of seven days between each treatment. The investigational products (IP) were administered at the trial site under the supervision of the study team. Both treatments were followed by an inspection of the oral cavity and of the hands.

Blood sampling was performed over 48h post-dose to characterize PK parameters. 20 blood samples were collected at specified time points (Study A: 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours. In Study B: 0, 0.50, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours) following the administration of the study drug in each period of both trials.

2.4 Analytical methods

Plasma concentrations of rivaroxaban were determined using a validated analytical Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method. The method utilized protein precipitation of blood plasma samples. After dilution of the supernatant, processed samples were trans-

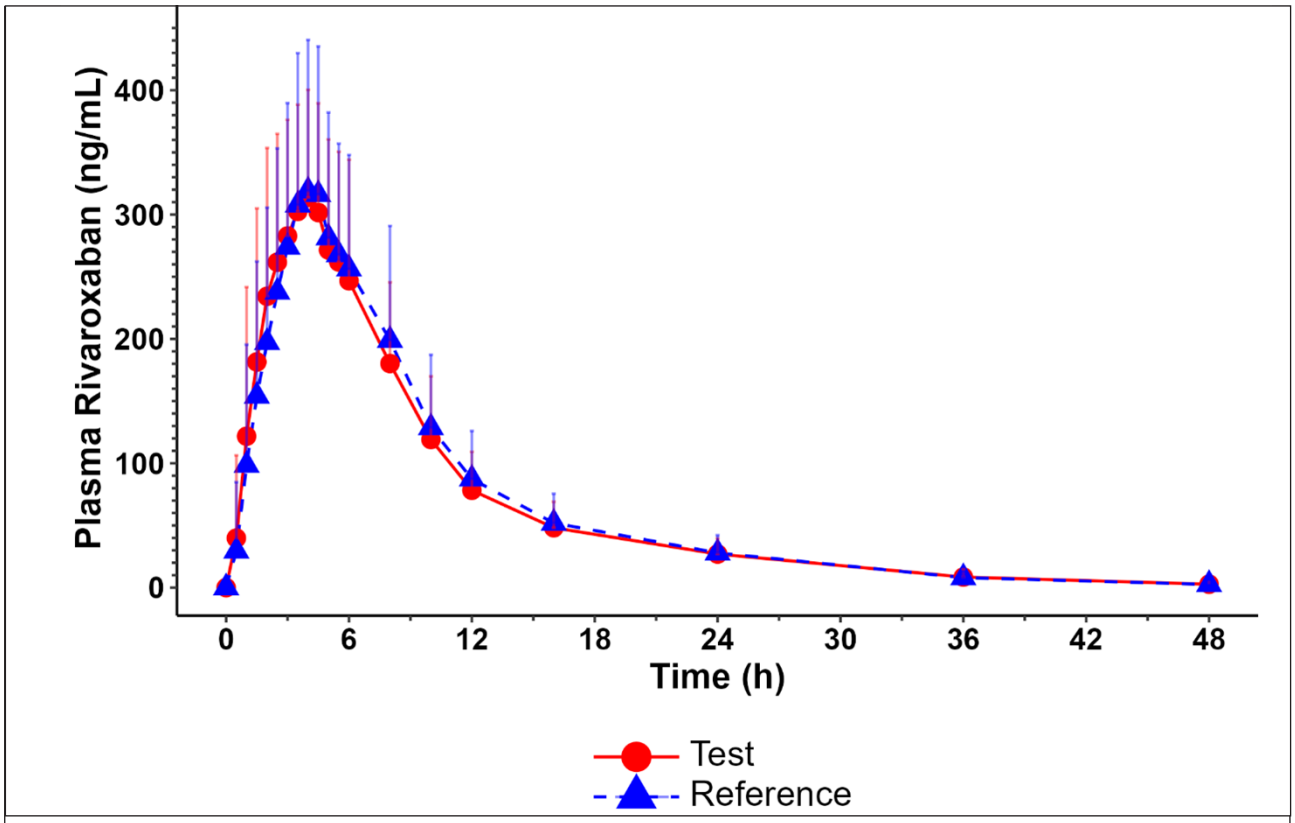

Figure 2. *Rivaroxaban plasma concentration in study B – Mean (+SD) Rivaroxaban plasma concentration - time profile (linear scale) following single oral administration of Rivaroxaban 20 mg tablet (Test) and Xarelto® 20 mg tablet (Reference) in Study B*

ferred for analysis with positive scan mode. The calibration range has been set to 1.00 to 500 ng/mL.

2.5 Pharmacokinetic and statistical analysis

The primary PK parameters used to assess bioequivalence included the area under the plasma concentration-time curve from 0 to infinity (AUC_{inf}), the area under the plasma concentration-time curve from 0 to the last measurable concentration (AUC_t), and the C_{max}. The ratio of the geometric means (GMR) of the test formulation to the reference formulation for each of these parameters was calculated, and 90% confidence intervals (CIs) were constructed. Bioequivalence was concluded if the 90% CIs for the test/reference ratios for AUC_{inf}, AUC_t, and C_{max} were within the predefined bioequivalence range of 80.00% to 125.00%.

Statistical analysis was performed on quality assured data, with unbalanced groups, if necessary, from participants in the statistical dataset. The PROC GLM procedure from SAS® (version 9.4 or later) was used to calculate the PK parameters and bioequivalence assessment.

Before the analysis, PK and Statistical Datasets were defined. PK Dataset included subjects from whom C_{max} and AUC parameters can be estimated for both periods, and those who complied with protocol requirements or had non-impactful deviations. Statistical Dataset excluded subjects with pre-dose concentrations >5% of C_{max} or very low plasma concentrations (<5% of reference product's geometric mean AUC). Otherwise, it was considered identical to the PK dataset.

Descriptive statistics were used to summarize the baseline characteristics of participants. The PK parameters (AUC_{inf}, AUC_t, and C_{max}) were log-transformed, and analysis of variance (ANOVA) was used to evaluate the effect of treatment (test vs. reference), period, and sequence on the PK parameters. The 90% CIs for GMRs were calculated to assess bioequivalence.

Safety assessments encompassed continuous monitoring of adverse events (AE) and overall health status, with scheduled evaluations of vital signs and body temperature conducted at predefined intervals throughout the study duration. AE data listing included AEs onset and resolution date/time, duration, time from dosing, severity,

Table II. *Pharmacokinetic parameters of Test and reference Products*

	Study A (10 mg)				Study B (20 mg)			
	T/R ratio [%]	Lower Limit CI [%]	Upper Limit CI [%]	CV_{intra} [%]	T/R ratio [%]	Lower Limit CI [%]	Upper Limit CI [%]	CV_{intra} [%]
AUC_t (hr*ng/mL)	97.32	93.66	101.12	10	98.35	94.93	101.91	8
AUC_{inf} (hr*ng/mL)	97.35	93.74	101.10	10	98.61	95.26	102.08	8
C_{max} (ng/mL)	90.39	84.56	96.61	18	95.98	91.54	100.63	11

Point estimates and 90 % confidence intervals of pharmacokinetic parameters: comparison of Test vs. Reference (T/R) in Study A (n=42) and Study B (n=30). Cl= confidence interval

relationship to the IMP, outcome, and the action taken to the IMP and to treat the AE. All safety measures were evaluated using descriptive statistics. For safety assessment Safety Dataset was used, which included subjects who received at least one administration of any study treatment.

2.6 Monitoring and Ethics

Monitoring in the clinical trials was performed in accordance with the requirements of the ICH GCP (R3) guideline [7] and based on the monitoring plan. Source data verification (SDV) was performed for 100% of data obtained during the clinical trials on-site. The studies were performed in compliance with European Union Directive 2001/20/EC, applicable national statutory requirements, the Declaration of Helsinki, and ICH-GCP including the archiving of essential documents. The clinical trials were only initiated after receiving positive opinion from the Independent Ethics Committee and approval from the national health authority (Health Canada) was received for clinical trial protocols, subject information, including the Informed Consent Forms (ICF), as well as any subsequent amendments. Optimum Ethics Review Board, Canada, issued the Ethics Review Board Approval form for protocols No. 2019-4695 (Study A) and No. 2019-4694 (Study B) on 06/May/2020.

Informed consent was obtained from all subjects involved in the studies, prior to the first study-related activities. Every participant had the right to refuse further participation in the clinical trials at any time and without giving reasons. Participants were informed in the ICF that they would not receive any medical benefit from their participation since they were healthy and did not need treatment with this medical substance.

The studies were conducted at Pharma Medica Research Inc., with registered office at 6100 Belgrave Road, Mississauga, Ontario, L5R 0B7, Canada.

3. Results

3.1 Subject disposition and demographic characteristics

In Study A using the 10 mg formulation of the test and reference product, 42 healthy male participants were enrolled, and all completed the study. In case of study B with the 20 mg doses, 30 male participants were enrolled and completed the study. Accordingly, 42 (Study A) or 30 (Study B) participants received the test product, and 42 or 30 participants received the reference product respectively in a cross-over design. There were no drop-out participants throughout the studies.

The average age of the participants was 46 (Study A) and 44 (Study B) years. Racially, in both studies mostly Caucasian participants were included, with a higher proportion of Black or African American participants (36.7%) in study B. BMI ranges were similar across both studies, with means of 26.6 kg/m² and 26.2 kg/m², respectively.

3.2 Pharmacokinetic analyses

The mean plasma concentration time profiles for rivaroxaban following a single oral administration of rivaroxaban 10 mg tablet (T) and Xarelto® 10 mg tablet (R) under fasting conditions to subjects of the analysis set are presented in Figure 1. The statistical dataset was identical to the analysis dataset, comprising 42 subjects. The mean plasma concentrations of the test and reference products over time were found to be virtually superimposable.

The mean (+SD) plasma concentration time profiles of rivaroxaban following a single oral admin-

istration of rivaroxaban 20 mg tablet (T) and Xarelto® 20 mg tablet (R) under fed conditions to subjects of the analysis set are presented in Figure 2. The statistical dataset was identical to the analysis dataset, comprising 30 subjects.

In Study A, the GMRs for AUC_t and C_{max} were 97.32% and 90.39%, respectively, with 90% CIs within the bioequivalence range. In Study B, the GMRs for AUC_t and C_{max} were 98.35% and 95.98%, respectively, also within the bioequivalence range. The 90% CIs of the relative mean plasma rivaroxaban AUC_t and C_{max} of the test to reference products in both studies were between 80.00 and 125.00%. In both studies nearly 100% of AUC_{inf} was covered by AUC_t as presented in Table I and Table II.

ANOVA did not detect relevant difference in any of the PK parameters for period, treatment, or sequence effects. Both studies demonstrated that the test formulations of rivaroxaban were bioequivalent to the reference formulations, indicating similar absorption and exposure profiles.

3.3 Safety and tolerability outcomes

The safety evaluation of rivaroxaban in two studies (Study A and Study B) demonstrated that the drug was generally well-tolerated by healthy male subjects. In Study A (10 mg dose), 2 subjects (4.8%) reported a total of two TEAEs, both of which were headaches. One TEAE was assessed as related to the study drug (treatment B), while the other was not. All AEs were mild in severity and resolved without intervention. No serious adverse events (SAEs) or drop-outs due to AEs were reported.

In Study B (20 mg dose), two subjects (6.7%) reported a total of two TEAEs, both of which were chromaturia (discolored urine). Both events were assessed as related to the study drug (treatment A), were mild in severity, and resolved without intervention. Similar to Study A, no SAEs or drop-outs due to AEs were reported.

Overall, the studies indicated that rivaroxaban was well-tolerated, with only mild AEs that resolved without intervention, and no significant impact on the safety of the subjects or the integrity of the study results.

4. Discussion

The BE studies of rivaroxaban 10 mg and 20 mg filmcoated tablets (Gedeon Richter Plc., Hungary; brand names: Kardatuxan, Riqulatron, or Rivaroxaban Richter) confirmed that both strengths are bioequivalent to the reference products, Xarelto® 10 mg and 20 mg filmcoated tablets (Bayer AG, Germany). In both studies, the one conducted under fasting conditions for the 10 mg strength, as well as the one conducted under fed conditions for the 20 mg strength, the 90% CIs for the relative mean plasma rivaroxaban AUC_t and C_{max} values were well within the accepted 80.00–125.00% range (97.32% and 90.39%, respectively, for the 10 mg strength, and 98.35% and 95.98%, respectively, for the 20 mg strength). These results clearly demonstrate that the test formulations achieve the same systemic exposure as the reference products under the recommended administration conditions. Moreover, both formulations were well tolerated by the healthy male volunteers, with no unexpected safety events further supporting the reliability of the data.

The study designs were consistent with EMA's product-specific guidance for rivaroxaban filmcoated tablets [6], FDA's general bioequivalence requirements for solid oral dosage forms [9] and Health Canada's comparative bioavailability guidance [10], as well. The carefully outlined study design take in consideration the regulatory requirements deriving from the characteristics of rivaroxaban- the CV_{intra} of the active substance, its safety implications on the female population, as well as the dose-dependent limitation of absorption, as described previously- designing in conclusion a two-way, two-period, two-treatment, single dose cross-over study, under fasting conditions for the 10 mg strength, and fed conditions for the 20 mg strength. This regulatory alignment highlights the strength of the data and their suitability for global submissions.

As with all bioequivalence studies, certain inherent constraints apply. One such limitation is the use of healthy volunteers and single-dose administration, which does not compare pharmacokinetics of the test and reference formulation when administered over a long period of time. However, the guidelines and regulatory requirements of proving bioequivalence clearly states that in case the rate and extent of absorption and elimination of the test and reference products are similar within pre-specified limits, the minimal observed differences have no clinical relevance, no safety or efficacy implications, and the long-term use of the test (generic) product is just as safe and just as efficient as the reference (originator) product. Conclusively, proving similar pharmacokinet-

ics for a single-dose administration of our rivaroxaban formulation does not diminish the strength of the conclusion, and complies with the regulatory standards. Another limitation is the fact that bioequivalence guidelines recommend including both male and female subjects, whereas our study population consists of only healthy males. However, guidelines also emphasize the importance of minimizing the risk imposed to healthy volunteers and enable the exclusion of a patient population in case the administration of the drug would cause unnecessary threat. The potential reproductive toxicity, intrinsic risk of bleeding, as well as lactational risk of rivaroxaban resulted in our choice of only including males in the study, which conforms with regulatory requirements.

5. Conclusions

The results of these bioequivalence studies show that Rivaroxaban 10 mg and 20 mg film-coated tablets (Gedeon Richter Plc., Hungary) are equivalent to Rivaroxaban 10 mg and 20 mg film-coated tablets (Bayer AG, Germany) respectively.

Overall, the findings provide compelling evidence that the generic rivaroxaban formulations developed by Gedeon Richter are reliable, effective, and safe alternatives to the reference products. The results demonstrate that the test formulations provide the same rate and extent of absorption as the reference products under the recommended fed and fasting conditions.

By adhering to internationally harmonized standards, the studies provide confidence that the results are not only valid in the European context but also relevant for other major regulatory jurisdictions. This strengthens the case for broad acceptance of the generic formulations and facilitates their potential availability across multiple markets.

This ensures therapeutic equivalence and supports clinical interchangeability. Rivaroxaban 10 mg and 20 mg film-coated tablets by Gedeon Richter offer the healthcare system and patients a high-quality alternative with the same efficacy and safety profile as the originator.

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