COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rivaroxaban SUN 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets (rivaroxaban)

NL/H/5140/001-004/DC

Date: 13 February 2024

This module reflects the scientific discussion for the approval of Rivaroxaban SUN 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised on 12 January 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BE	Bioequivalence
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
HPLC	High-Performance Liquid Chromatography
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NF	National Formulary
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
XRD	X-ray Diffraction

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivaroxaban SUN 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets, from Sun Pharmaceutical Industries Europe B.V.

Rivaroxaban SUN has the following indications at different strengths:

Rivaroxaban SUN 2.5 mg
Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, the product is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Co-administered with acetylsalicylic acid (ASA), the product is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

Rivaroxaban SUN 10 mg
The product is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

The product is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Rivaroxaban SUN 15 mg
Adult population
The product is indicated for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. The product is indicated for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population
The product is indicated for treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

Rivaroxaban SUN 20 mg
Adults
The product is indicated in prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Paediatric population
The product is indicated in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The product is indicated in the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Xarelto 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EMEA/1/08/472-001) since 30 September 2008 by Bayer AG. The additional strengths (15 and 20 mg) were registered on 9 December 2011.

The concerned member states (CMS) involved in this procedure were France, Germany, Italy, Poland, Romania, Spain, and United Kingdom (Northern Ireland).

II. QUALITY ASPECTS

II.1 Introduction

Rivaroxaban SUN 2.5 mg, 10 mg, 15 mg and 20 mg are dose-proportional film-coated tablets. Each film-coated tablet contains 2.5 mg, 10 mg, 15 mg and 20 mg rivaroxaban. The four strengths of the film-coated tablets can be distinguished by the different sizes, colours and debossing and are as follows:

Rivaroxaban SUN 2.5 mg
The 2.5 mg strength tablets are light yellow, film coated, round of 6.0 mm in diameter, debossed with "□" on one side and "2.5" on the other side.

Rivaroxaban SUN 10 mg
The 10 mg strength tablets are pink, film coated, round of 6.0 mm in diameter, debossed with "□" on one side and "10" on the other side.

Rivaroxaban SUN 15 mg
The 15 mg strength tablets are red, film coated, round of 6.0 mm in diameter, debossed with "□" on one side and "15" on the other side.

Rivaroxaban SUN 20 mg
The 20 mg strength tablets are dark red, film coated, round of 6.0 mm in diameter, debossed with "□" on one side and "20" on the other side.

The excipients are:

Tablet core – cellulose, microcrystalline (E460), hypromellose 2910 (E464), lactose monohydrate, low substituted hydroxypropyl cellulose (E463), croscarmellose sodium (E486), sodium lauryl sulfate (E487) and magnesium stearate (E572).
Film-coat - Hypromellose 2910 (E464), lactose monohydrate, macrogol 4000 (E1521), titanium dioxide (E171), iron oxide yellow (E172) (strength 2.5 mg and 10 mg), iron oxide black (E172) (strength 2.5 mg), Iron oxide red (E172) (strength 15 mg and 20 mg) FD & C Red 40 (E129) (strength 10 mg) and FD & C Blue 1 (E133) (strength 10 mg) carmine (E120) (strength 15 mg) and FD & C Yellow 6 (E110) (strength 15 mg).

The film-coated tablets are packed in clear polyvinyl chloride/polyvinylidene chloride aluminium (PVC/PVDC/Al) blisters, in cartons.

II.2 Drug Substance

The active substance is rivaroxaban (micronized), an established active substance described in the European Pharmacopoeia (Ph.Eur.). Rivaroxaban is a white to yellowish crystalline powder. Rivaroxaban is soluble in DMSO and DMF, slightly soluble in acetone and PEG 400 and practically insoluble in water. Rivaroxaban exhibits polymorphism between three forms. Rivaroxaban is the active enantiomer with a chiral centre (S configuration). The applicant identifies the S- and the potential R-enantiomers by Chiral High-performance liquid chromatography (HPLC). For this product, polymorphic form I is consistently produced and verified by the applicant or marketing authorisation holder (MAH) through x-ray diffraction (XRD).

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the MA) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Rivaroxaban micronized is synthesised in two reaction steps. The first step is a drug substance synthesis step and the second a purification step. During the synthesis, one isolated intermediate is found. All starting materials are acceptable and in line with ICH Q11. Moreover, the level of impurities originating from the synthesis of the starting materials has been proven not to have a significant effect on the impurity profile of the final drug substance.

Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. general USP requirements and additional

tests for identification by Chiral HPLC, residual solvents, particle size, assay, related compounds and chiral purity. Batch analytical data demonstrating compliance with this specification have been provided for seven full scaled batches. The presented batch data comply with the specification requirements.

Stability of drug substance

Stability data on the active substance have been provided for seven full scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for five years. There are no specific storage conditions required.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batches used in Bioequivalence (BE) studies is similar to the marketed product. The proposed QC dissolution method is acceptable, and the discriminating power of the QC dissolution method has been demonstrated. *In vitro* dissolution studies support the observed *in vivo* bioequivalence (BE).

Comparative dissolution profiles in buffer at 1.2 pH (0.1 HCl), 4.5 pH (acetate) and 6.8 pH (phosphate) without surfactants are included demonstrating similarity in dissolution. Similarity of dissolution profiles is demonstrated ($f_2 > 50$), at all conditions, between additional strengths (2.5 mg and 15 mg) and the corresponding strengths used for BE testing (10 mg and 20 mg).

To support the application, the MAH has submitted two single-dose (10 mg, fasting, and 20 mg, fed) BE studies. The MAH performed two additional single-dose (2.5 mg, fasting, and 15 mg, fed) BE studies.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two commercial-scaled batches in accordance with the relevant European guidelines. Tablets are manufactured by wet granulation followed by milling, drying, blending, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two commercial-scaled batches.

Control of excipients

The excipients comply with Ph.Eur./National Formulary (NF) requirements except for the excipients that are part of the film-coating mixture. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, water content, content uniformity, dissolution, assay, related compounds, residual solvents and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three exhibit batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three exhibit batches per strength stored at 25°C/ 60% RH (18 months in the case of 2.5 mg; 24 months for the 15 mg and 20 mg strengths; 44-46 months for the 10 mg strength) and 40°C/ 75% RH (6 months for all strengths) and packed in PVC/PVDC-aluminium blisters. The stability was tested in accordance with applicable European guidelines. Photostability studies were performed for one pilot batch of the 2.5 mg, 10 mg, 15 mg and 20 mg strengths in accordance with ICH recommendations and showed that the product is stable when exposed to light. On the basis of the data submitted, a shelf-life was granted of 24 months.

Stability data on crushed tablets in water/apple sauce have been provided. Similar studies have been conducted to demonstrate stability of crushed tablets in water for administration via a gastric tube.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rivaroxaban SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Post-Approval Stability Protocol and Stability Commitments - At least one batch annually, if manufactured, will be placed on the long-term stability program.
- Perform the process validation on the first three commercial batches of each strength.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivaroxaban SUN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xarelto which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rivaroxaban, micronized is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Rivaroxaban 10 mg under fasting conditions and 20 mg under fed conditions film-coated tablets (Taro Pharmaceutical Industries, Israel) was compared with the pharmacokinetic profile of the reference product Xarelto 10 mg and 20 mg film-coated tablets (Bayer AG, Germany). The applicant carried out two additional single dose bioequivalence studies, one for the 2.5 mg tablet under fasting conditions and one for the 15 mg tablet under fed conditions.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. The comparative dissolution between Rivaroxaban 10 mg and 20 mg strengths (bio batches, test product) versus the respective reference product was performed in three different pH media: pH 1.2, pH 4.5 (QC media) and pH 6.8. The f_2 values of all tested couples (test vs reference), in all pH media, are less than 50. According to CPMP/EWP/QWP/1401/98 Rev. 1: "In the event that the

results of comparative i*n vitro* dissolution of the bio-batches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails".

Bioequivalence studies

Study 1 – single-dose, 10 mg under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 19-44 years. Each subject received a single dose (10 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.33, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

The design of the study is acceptable.

Rivaroxaban 10 mg may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of rivaroxaban 10 mg. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results

Three subjects were withdrawn from the study: two subjects dropped out after period 1 due to an adverse event (pruritus (itch), 5 days post dosing) and failure to report to the clinical facility during the day of admission in period 2. One subject dropped out during admission to period 2 due a positive alcohol breath test. 43 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 10 mg under fasted conditions.

Treatment N=43	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	1556 ± 380 (24.4%)	1596 ± 385 (24.1%)	203 ± 61.3 (30.2%)	2.33 (1.00-4.50)
Reference	1482 ± 371 (25.1%)	1525 ± 376 (24.6%)	185 ± 50.4 (27.2%)	2.00 (1.00-5.00)
***Ratio (90% CI)**	1.05 (1.00 - 1.10)	1.05 (1.00 - 1.09)	1.08 (0.98 - 1.18)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – single-dose, 20 mg, under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fed conditions in 26 healthy male subjects, aged 20-44 years. Each subject received a single dose (20 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water exactly 30 minutes after the start of a high-fat, high-calorie breakfast (262 kcal cholesterol, 162 kcal protein, 563 kcal fat), after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.5 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

The design of the study is acceptable.

Results

26 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 20 mg under fed conditions.

Treatment N=26	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	3167 ± 826 (26.1%)	3205 ± 836 (26.1%)	394 ± 116 (29.5%)	3.50 (1.00 - 10.00)
Reference	3233 ± 723 (22.4%)	3289 ± 727 (22.1%)	410 ± 102 (24.8%)	3.50 (1.00 - 8.00)
***Ratio (90% CI)**	0.97 (0.93 - 1.01)	0.96 (0.93 - 1.00)	0.95 (0.90 - 1.01)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3 – single-dose, 2.5 mg, under fasting conditions

Design

A single-dose, randomised, three-period, two-treatment, three-sequence, crossover, double-blind bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-43 years. Each subject received a single dose (2.5 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were three dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

The design of the study is acceptable.

Results
A total of 36 subjects entered the study. Four subjects were withdrawn from the study. Two subjects dropped out after period 1 due to failure to report to the clinical facility during the day of admission in period 2 and were therefore, withdrawn from Period 2 only. Two subjects dropped out after period 2 due to failure to report to the clinical facility during the day of admission in period 3 and were therefore, withdrawn from period 3. 34 subjects were eligible for pharmacokinetic analysis for period 2 and 32 for period 3.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 2.5 mg under fasted conditions.

Treatment	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test N = 34	479 ± 154 (32.1%)	490 ± 158 (32.3%)	73.8 ± 28.3 (38.3%)	2.225 ± 1.440 (64.7%)
Reference 1 N = 33	491 ± 155 (31.6%)	501 ± 158 (31.6%)	79.1 ± 27.8 (35.2%)	1.803 ± 0.979 (54.3%)
Reference 2 N = 33	475 ± 109 (23.0%)	485 ± 111 (22.8%)	76.1 ± 16.3 (21.4%)	1.949 ± 0.961 (49.3%)
***Ratio Reference 1 (90% CI)**	0.98 (0.92 – 1.04)	0.98 (0.92 – 1.04)	0.92 (0.84 – 1.01)	-
***Ratio Reference 2 (90% CI)**	1.00 0.95 – 1.05	1.00 0.95 – 1.05	0.98 0.91 – 1.05	-

$AUC_{0-\infty}$ Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

**ln-transformed values*

Study 4 – single-dose, 15 mg, under fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fed conditions in 18 healthy male (31) and female (5) subjects, aged 19-42 years. Each subject received a single dose (15 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water exactly 30 minutes after the start of a high-fat, high-calorie breakfast (262 kcal cholesterol, 162 kcal

protein and 563 kcal fat), after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of at least 5 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

The design of the study is acceptable.

Rivaroxaban 15 mg and 20 mg are to be taken with food due to a reduced absorption of the 15 mg and 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food, increases in mean AUC were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability.

Results
A total of 36 subjects entered the study. Two subjects were discontinued from the study. Two subjects dropped out in period 1 due to a mild adverse event (vomiting) and another was lost to follow-up. 34 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 15 mg under fed conditions.

Treatment N=34	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	2524 ± 626 (24.8%)	2551 ± 625 (24.5%)	331 ± 73.1 (22.1%)	3.83 (1.00 - 5.50)
Reference	2694 ± 694 (25.8%)	2715 ± 702 (25.9%)	353 ± 68.9 (19.5%)	3.33 (1.00 - 5.00)
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	0.94 (0.90 – 0.98)	0.93 (0.89 – 0.98)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies (studies 1-4):
The 90% confidence intervals calculated (studies 1-4) for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg, is considered bioequivalent with Xarelto 2.5, 10, 15 and 20 mg.

Rivaroxaban 15 mg and 20 mg are to be taken with food due to a reduced absorption of the 15 mg and 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food, increases in mean AUC were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Analytical/statistical methods
The analytical methods has been adequately validated and is considered acceptable for analysis of the plasma samples of all four studies. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rivaroxaban SUN.

Table 5. Summary table of safety concerns as approved in RMwP

Important identified risks	Haemorrhage
Important potential risks	Embryo-foetal toxicity
Missing information	Patients with severe renal impairment (CrCl < 30 mL/min). Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir). Remedial pro-coagulant therapy for excessive haemorrhage. Pregnant or breast-feeding women. Patients with atrial fibrillation (AF) and a prosthetic heart valve. Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting. Patients with significant liver diseases (severe hepatic impairment/Child Pugh C). Patients < 18 years.

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use rivaroxaban SUN. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Rivaroxaban SUN and providing guidance on how to manage that risk. The physician educational pack should contain The Summary of Product Characteristics, Prescriber Guide and Patient Card.

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory.

The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations

- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance
    - The need for intake of the 15 mg and 20 mg tablets with food
    - Necessity to carry the Patient Card that is included in each pack, with them at all times
    - The need to inform Health Care Professionals that they are taking Rivaroxaban SUN if they need to have any surgery or invasive procedure.

The MAH shall also provide a Patient Card in each medicine pack.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xarelto. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies with each strength that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of two bridging reports. The first makes reference to the innovator Xarelto, EU/1/08/472/001-039 and EU/1/08/472/041-049. The bridging report submitted by the MAH has been found acceptable; bridging is justified for content of the leaflet.

The second bridging reported makes reference to Esomeprazole, NL/H/4120/001-002/DC as parent leaflet. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both design and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rivaroxaban SUN 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Xarelto 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets. Xarelto is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rivaroxaban SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 January 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5140/ 1-4/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	Yes	22-11-2023	Approved	-
NL/H/5140/ 1-4/IA/002	Change in the name and/or address of the marketing authorisation holder	No	22-11-2023	Approved	-