CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Rufixalo 2.5, 10, 15, 20 mg film-coated tablet
RIVAROXABAN

HU/H/0711/001-004/DC

Date: 10. 08. 2022

This module reflects the scientific discussion for the approval of Rufixalo 2.5, 10, 15, 20 mg film-coated tablets. The procedure was finalised at 08/08/2022. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rufixalo 2.5, 10, 15, 20 mg film-coated tablets from Alkaloid-Int d.o.o.

Indications:

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

10 mg tablets:
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

15 mg and 20 mg tablets:
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.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
Paediatric population
15 mg film-coated tablets:
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.
20 mg film-coated tablets:
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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xarelto 10 film-coated tablet by Bayer Pharma AG, registered since 30-9-2008 (published 2-10-2008) and the Xarelto 2.5, 15 and 20 mg film-coated tablets, since 14-12-2011. The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia and Slovenia. The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

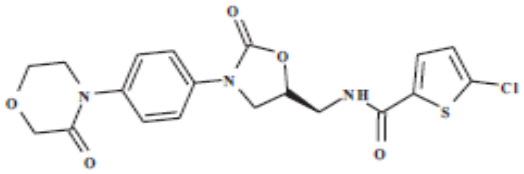
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Rufixalo 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by PharOS Ltd., Greece.
Reference products are Xarelto film-coated tablets (containing rivaroxaban as active ingredient) which were the original products of Bayer AG.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure in the initial phase of the marketing authorisation procedure, which has been changed to a certificate of suitability (CEP), issued in the meantime, with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: rivaroxaban
Chemical name: 5-Chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1, 3-oxazolidin-5-yl] methyl] thiophene-2-carboxamide
Structure:



The active substance is white, to yellow powder, practically insoluble in water, freely soluble in Dimethyl sulfoxide, practically insoluble in anhydrous ethanol and in heptane. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by NMR, MS, XRD and elemental analysis. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specifications have been set for identification by XRD, residual solvents, formic acid, particle size distribution and microbial impurities.
The Ph. Eur. specification includes the following tests for rivaroxaban: description, solubility, identification by IR and by HPLC, water content, sulphated ash, related substances, assay, and enantiomeric purity.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period and the packaging material (double polyethylene bag in polyethylene drum, in nitrogen atmosphere) has been mentioned on the CEP.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop film-coated tablets containing rivaroxaban as drug substance in 2.5 mg, 10 mg, 15 mg and 20 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product Xarelto film-coated tablets, the branded original products of Bayer AG.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

The 2.5 mg product is light yellow, round biconvex tablet, debossed with "2.5" on one side and plain on the other side.
The 10 mg product is light red, round biconvex tablet debossed with "10" on one side and plain on the other side.
The 15 mg product is red, round biconvex tablet, debossed with "15" on one side and plain on the other side.
The 20 mg product is brown-red, round biconvex tablet, debossed with "20" on one side and plain on the other side.

The excipients used in the finished product are sodium laurilsulfate, lactose, poloxamer, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, the film coating consist of hypromellose, titanium dioxide, macrogol as well as yellow iron oxide in the 2.5 mg strength and red iron oxide in the other strengths. All excipients used comply with their respective European Pharmacopoeia monograph or EU guidelines. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure systems of the product are Aluminium-PVC/PE/PVdC blisters. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 3 years with no special storage conditions** is approved.
The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of rivaroxaban are well known. As rivaroxaban is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

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

III.3 Discussion on the non-clinical aspects

This product is a generic formulation of Xarelto which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional nonclinical 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 is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.
For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

According to the Product Specific Guidance of rivaroxaban “Since there is a different food effect resulting in different food recommendations for the lower (10 mg) and the higher (15 and 20 mg) strengths, two studies are required. One study under fasting conditions with the 10 mg strength and one study under fed conditions with the 20 mg strength are recommended.”
To support the application two pivotal single-dose bioequivalence studies were submitted with the strength of 10-20 mg film-coated tablets.
The first study was conducted with the 10 mg film-coated tablets in heathy male volunteers in fasting conditions, the second study was conducted with the 20 mg film-coated tablets in heathy

male volunteers in fed conditions.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

A biowaiver was requested for the 2.5 mg and the 15 mg formulation of Rivaroxaban based on the above bioequivalence studies.

Biowaiver

In accordance with the 'Guideline on the investigation of bioequivalence', if the application concerns several strengths of the active substance, a bioequivalence study investigating only one strength may be acceptable if all the following conditions are fulfilled:
a) The pharmaceutical products are manufactured by the same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).

d) Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

With respect to the above conditions it can be concluded that:
All strengths of the test product are manufactured with the same manufacturing process. The qualitative composition of Rivaroxaban film-coated tablets 15 and 20 mg strengths is the same and their composition is quantitatively proportional while the qualitative composition of Rivaroxaban film-coated tablets 2.5 and 10 mg strengths is identical and their composition although is not directly proportional condition c is still considered fulfilled since condition i) and iii) above apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered.

As the SmPC of the originator Xarelto it is stated: "Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality."
The biowaiver request can be accepted to the 2.5 mg and the 15 mg Rivaroxaban film-coated tablets with the submitted f2 statistics.

Bioequivalence studies

BIOEQUIVALENCE STUDY-I

The study was a single centre, randomized, single dose, laboratory-blinded, 2-treatment, 2-period, 2-sequence, crossover design in 42 healthy male subjects. The following investigational products were administered under fasting conditions: Test: 1 x Rivaroxaban 10 mg film-coated tablet and Reference: 1 x Xarelto® (rivaroxaban) 10 mg film-coated tablet. A washout period of seven (07) days was kept between each consecutive dosing period.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1432.73 (±302.73)	1472.62 (±310.04)	165.07 (±41.97)	2.00 (0.67-4.00)
Reference	1479.89 (±298.31)	1517.18 (±303.86)	174.96 (±44.34)	2.17 (0.67-5.00)
***Ratio (90% CI)**	96.78 (92,48 -101,27)		94.92 (87.37 – 103.12)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

The extrapolated AUC was not higher than 20% in any subject.
T_{max} was not observed in any subject in the first sample time, which means that the C_{max} has been characterised adequately.

Conclusion
Bioequivalence is shown appropriately. No t_{max} was observed in any subject in the first sample time. Individual plasma concentration/time curves were presented in linear/linear and log/linear scale

BIOEQUIVALENCE STUDY- II

The study was a pivotal, single center, randomized, single-dose, laboratory-blinded, two-period, two-sequence, crossover comparative bioequivalence study of Rivaroxaban 20 mg film-coated tablets (DOC) and Xarelto® 20 mg film-coated tablets (Marketing Authorization Holder: Bayer AG, Germany) in healthy male volunteers under fed conditions. The two periods were separated by a wash-out period of 7 calendar days

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	2931.13 (±687.60)	2971.98 (±688.30)	387.65 (±103.10)	4.00 (1.00, 8.00)
Reference	2943.96 (±702.88)	2979.58 (±705.45)	386.31 (±85.42)	2.83 (1.00, 6.10)
***Ratio (90% CI)**	99.77 (95.04 – 10.74)	-	99.33 (92.68 – 106.46)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

All subjects had plasma concentration curves where the residual area for the Test and Reference formulation was < 20%. Therefore, the sampling schedule covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure.
Plasma levels were below the LOQ (1.00 ng/mL) in all samples collected prior to dosing. The wash-out period between doses was considered appropriate.
The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-T} were all within the acceptance range of 80.00 to 125.00%. No statistically significant treatment, sequence or period effects were observed for the ln-transformed C_{max} and AUC_{0-T} data.

Conclusion
Bioequivalence was shown appropriately. No t_{max} was observed in any subject in the first sample time. Individual plasma concentration/time curves were presented in linear/linear and log/linear scale.

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence studies Rufixalo 10 mg and 20 mg film-coated tablets are considered bioequivalent with Xarelto 10 mg and 20 mg film-coated tablets (manufacturer: Bayer AG).
The biowaiver request can be accepted to the 2.5 and 15 mg Rivaroxaban film-coated tablets.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.4 Clinical efficacy

No new efficacy study has been performed by the applicant.

IV.5 Clinical safety

No new safety data have been submitted by the applicant.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version 0.4, sign-off 18.07/2022), 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 Rufixalo 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets.

Safety specification as proposed by the Applicant

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
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)

The summary table of safety concerns is adequate, since it is in line with the latest version of originator's RMP (Xarelto, RMP version 12.4, 01-02-2021. See Xarelto H944-X-074-G: Assessment Report. https://www.ema.europa.eu/en/documents/variation-report/xarelto-h-c-944-x-0074-g-epar-assessment-report-variation_en.pdf)

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

However, the innovator has follow-up forms for Xarelto as routine pharmacovigilance activities:
- Liver related adverse events
- Renal impairment / renal failure
- Severe hypersensitivity
- Severe skin reactions

Applicant implemented the adverse event follow-up forms into Part III. 1 Routine pharmacovigilance activities and into Annex 4 as well.

Risk minimisation measures

- **Additional risk minimisation measures (including educational material)**

The applicant proposes additional risk minimisation measures for the important identified risk Haemorrhage:

- Educational material for prescribers (Prescriber Guide)
- Patient alert cards

The MAHs shall provide an Educational material for prescribers (Prescriber Guide) prior to launch, targeting all physicians who are expected to prescribe/use the product. The Prescriber guide encourages the HCPs to use this tool in conjunction with the Summary of Product Characteristics during every rivaroxaban consultation in order to minimize the risk of hemorrhage. The educational material is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk.

The MAHs 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 Alert Card that is included in each pack, with them at all times
- The need to inform Health Care Professionals that they are taking the product if they need to have any surgery or invasive procedure.

The MAHs shall also provide a Patient Alert Card in each medicine pack, the text of which is included in Annex III of Xarelto's product information (see EMA website https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf)

The submitted additional risk minimisation measures to address the risks associated with haemorrhage, including Educational material for prescribers (Prescriber guide) and Patient alert cards are considered appropriate.

Details of local dissemination and exact content of the educational materials should be agreed with the national competent authorities in the national phase of this decentralised procedure.

Conclusion on the submitted RMP

The submitted Risk Management Plan, version 0.4 signed 18/07/2022 is acceptable, as the name of the product has been changed from Rivaroxaban Alkaloid-INT to Rufixalo throughout of the RMP.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
Date of end of procedure + 5 years

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Xarelto 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets, CAP - EMEA/H/C/000944 and Drospirenone/ethinylestradiol 3 mg/0.03 mg film-coated tablets, NAP - HR/H/0137/001/DC; Xarelto 10 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Xarelto is a wellknown 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.