IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Rivaroxaban 15 mg film-coated tablets
Rivaroxaban
PA1226/016/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Rivaroxaban 2.5mg, 10mg, 15mg & 20mg Tablets, from Flynn Pharma Limited on 26th January 2024 for the following indications:

2.5 mg film-coated tablets:

- 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.
- 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 film-coated 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 film-coated tablets:

- Adults:
    - 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:
    - 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:

- Adults:
    - 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:
    - 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.

The originator product is Xarelto 2.5 mg, 10 mg, 15 mg & 20 mg film-coated tablets (EU/1/08/472/025, EU/1/08/472/007, EU/1/08/472/012 and EU/1/08/472/018), MAH: Bayer AG, 51368 Leverkusen, Germany, registered since 30/09/2008.

These products are subject to a prescription which may be renewed.

In support of this application, the applicant submitted data from three bioequivalence studies in accordance with current guidance.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product:	Rivaroxaban 15 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Rivaroxaban
Pharmacotherapeutic classification (ATC code)	B01AF01
Pharmaceutical form and strength(s)	15 mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1226/016/003
Marketing Authorisation Holder	Flynn Pharma Limited
MRP/DCP No.	IE/H/1243/003/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Rivaroxaban 2.5mg, 10mg, 15mg & 20mg Film-coated Tablets.

II.2 Drug substance

The active substance is Rivaroxaban, an established active substance described in the European/British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The tablets contain either 2.5mg, 10mg, 15mg or 20mg of Rivaroxaban.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

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

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturerss specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Rivaroxaban 2.5 mg, 10 mg, 15 mg, 20 mg, Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Xarelto 2.5 mg, 10 mg, 15 mg, 20 mg, film-coated tablets from Bayer AG, Germany, authorised via the centralised procedure (EU/1/08/472/) on the European market since 30/9/2008. No new preclinical data have been submitted. This is acceptable for this type of application.

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. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Rivaroxaban 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

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. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rivaroxaban is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Xarelto marketed by Bayer AG.

For this generic application, the applicant has submitted three bioequivalence studies in which the pharmacokinetic profile of the test products Rivaroxaban 2.5mg, 10mg, & 20mg Tablets compared with the pharmacokinetic profile of the reference product Xarelto 2.5 mg, 10 mg, and 20 mg Film-Coated Tablets. A biowaiver was sought for Rivaroxaban 15 mg Tablets which was justified.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Xarelto 2.5 mg, 10 mg, 15 mg & 20 mg film-coated tablets by Bayer AG.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Summary of Bioequivalence studies
In support of this application, the applicant has submitted the following bioequivalence studies:

Bioequivalence Study C1B00781
This open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting conditions was conducted to compare and evaluate the oral bioavailability of Rivaroxaban Film-Coated Tablets 2.5 mg and XARELTO (Rivaroxaban) Film-Coated Tablets 2.5 mg.

The study was conducted with 36 (31 completed) subjects in accordance with protocol.

A summary of pharmacokinetic results are presented below:

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** hr
Test	451.822 ± 145.561	467.138 ± 150.477	76.060 ± 21.220	2 (0.667 – 4.500)
Reference	462.121 ± 150.359	475.948 ± 154.469	77.428 ± 25.304	1.667 (0.667 – 5.500)
***Ratio (90% CI)**	98.44 (94.16 - 102.92)	n/a	99.70 (94.24 - 105.48)	n/a
CV (%)	10.325		13.102	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} canbe 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 whenAUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached (median range)

*Ratio of ln-transformed values of geometric means

Bioequivalence Study C1B00768
This open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting conditions was conducted to compare and evaluate the oral bioavailability of Rivaroxaban Film-Coated Tablets 10 mg and XARELTO (Rivaroxaban) Film-Coated Tablets 10 mg.

The study was conducted with 66 (61 completed) subjects in accordance with protocol.

A summary of pharmacokinetic results are presented below:

Treatment	**AUC_{0-t}**	**$AUC_{0-\infty}$**	**C_{max}**	**t_{max}**

	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} hr
Test	1185.725 ± 413.134	1210.656 ± 413.134	151.274 ± 46.155	2.167 (1.000 – 4.500)
Reference	1163.947 ± 370.980	1192.746 ± 377.633	150.274 ± 44.598	
***Ratio (90% CI)**	101.45 (97.88 – 105.14)	n/a	100.13 (94.27 – 106.35)	n/a
CV (%)	11.772		19.935	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} canbe 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 whenAUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached (median range)

*Ratio of ln-transformed values of geometric means

Bioequivalence Study C1B00770
This open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fed conditions was conducted to compare and evaluate the oral bioavailability of Rivaroxaban Film-Coated Tablets 20 mg and XARELTO (Rivaroxaban) Film-Coated Tablets 20 mg.

The study was conducted 27 subjects. This is acceptable to determine bioequivalence.

A summary of pharmacokinetic results are presented below:

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** hr
Test	2466.596 ± 490.986	2493.917 ± 484.960	317.954 ± 59.422	4.000 (2.000 – 4.667
Reference	2431.442 ± 472.630	2451.167 ± 467.373	321.187 ± 71.038	4.33 (1.00 – 4.667)
***Ratio (90% CI)**	100.98 (94.90 – 107.44)	n/a	99.09 (92.21 – 106 .48)	n/a
CV (%)	12.527		14.535	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} canbe 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 whenAUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached (median range)

*Ratio of ln-transformed values of geometric means

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits of 80.00 – 125.00%, show that the Test product Rivaroxaban 2.5 mg, 10 mg and 20 mg Film-Coated Tablets is bioequivalent with the Reference product Xarelto (Rivaroxaban Film-Coated Tablets) 2.5 mg and 10 mg under fasting conditions and to Xarelto (Rivaroxaban Film-Coated Tablets) 20 mg under fed conditions.

As the additional 15 mg strength of rivaroxaban meets the biowaiver criteria specified in current guidance, the results and conclusions from the bioequivalence studies can be extrapolated to the 15 mg strength.

IV.3 Pharmacodynamics

No new studies on pharmacodynamics have been submitted. As bioequivalence with the originator product has been demonstrated, additional data is not necessary.

IV.4 Clinical Efficacy

With the exception of the safety data submitted from the bioequivalence studies, no new safety data were submitted as part of this application.

The safety data from the bioequivalence studies showed that the test and reference product are equally well tolerated. No new or unexpected safety issues were raised from these studies.

IV.5 Clinical Safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. As bioequivalence with the originator product has been demonstrated, additional data is not necessary.

A risk management plan was submitted, 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 2.5 mg, 10mg, 15mg, 20mg film coated tablets.

Safety specification

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and a prosthetic heart valve

Routine pharmacovigilance activities are sufficient to identify and characterise risks. Additional risk minimisation measures in the form of a guide for healthcare professionals and a patient alert card are in place to minimise the risk of haemorrhage. Periodic safety update reports (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.

IV.6 Discussion on the clinical aspects

Data from the three clinical bioequivalence studies (2.5 mg, 10 mg and 20 mg strength) and the biowaiver request for the fourth strength (15 mg) have satisfactorily demonstrated bioequivalence between the test products of the applicant and the reference medicinal products.

The clinical overview is based on published literature data. This is acceptable since rivaroxaban is a well-known active substance and essential similarity is claimed to the reference product. This is considered sufficient for this type of application.

V. OVERALL CONCLUSIONS

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

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of data submitted considered that Rivaroxaban 2.5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets by Flynn Pharma Ltd demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted marketing authorisations to all four product strengths.

VI. REVISION DATE

05.012.2028