IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Rivaroxaban 15 mg film-coated tablets
Rivaroxaban
PA22865/010/002

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

Based on the review of the data on quality, safety, and efficacy, the HPRA has granted marketing authorisations for Rivaroxaban 10mg, 15mg, 20mg Film-coated tablets, from Renata Pharmaceuticals (Ireland) Limited, on 5th January 2024 for the following therapeutic indications:

For 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.

For 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 ischemic 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 to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

For 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.

With Ireland as the Reference Member State in this decentralised procedure, Renata Pharmaceuticals (Ireland) Limited applied for Marketing Authorisations for Rivaroxaban 10 mg, 15 mg & 20 mg film-coated tablets. There was one Concerned Member State involved in the procedure, Malta. The application was a generic application made according to Article 10(1) of Directive 2001/83/EC.

The originator product is Xarelto, 10 mg, 15 mg & 20 mg film-coated tablets (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.

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

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

Name of the product:	Rivaroxaban 15mg 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 tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/010/002
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1230/002/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Rivaroxaban 10mg, 15mg, 20mg Film-coated tablets.

II.2 Drug substance

The active substance is Rivaroxaban an established active substance described in the European 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 10 mg, 15 mg or 20 mg 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 manufacturer's 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 10 mg, 15 mg, 20 mg Film-coated tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of rivaroxaban are well-known. With the exception of data from two bioequivalence studies, no new clinical data are provided or are required for this type of application.

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

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

IV.2 Pharmacokinetics

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

Bioequivalence Study No. 305-20:
An open label, randomised, two-treatment, two-sequence, two-period, cross-over, single dose, oral bioequivalence study of Rivaroxaban 10 mg film-coated tablets (Test) of Renata Limited, Bangladesh and Xarelto (Rivaroxaban) 10 mg film-coated tablets (Reference) of Bayer AG, Germany in healthy, adult, human subjects under fasting conditions.

The study included 44 subjects of which 41 completed the study and were included in the statistical analysis of the parent, rivaroxaban.

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	1141.194±297.6840	1201.419±301.6262	164.443±41.3447	2.50(1.00-5.50)
Reference	1203.170±341.5974	1268.548±352.5527	181.559±57.3164	2.00 (0.67-4.00)
***Ratio (90% CI)**	95.72 (90.76-100.94)	NA	92.33 (86.68-98.34)	NA
CV (%)	14.4	NA	17.1	NA

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

*ln-transformed values

Bioequivalence Study No. 306-20:
An open label, randomised, two-treatment, two-sequence, two-period, cross-over, single dose, oral bioequivalence study of Rivaroxaban 20 mg film-coated tablets (Test) of Renata Limited, Bangladesh and Xarelto (Rivaroxaban) 20 mg film-coated tablets (Reference) of Bayer AG, Germany in healthy, adult, human subjects under fed conditions.

The study included 26 subjects of which 25 completed the study and were included in the statistical analysis of the parent, rivaroxaban.

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	2661.972±585.5050	2718.662±573.8800	392.445±87.5030	4.00(1.00-5.50)
Reference	2580.455±523.6889	2639.186±523.0722	391.151±82.3153	4.00(1.50-5.00)
***Ratio (90% CI)**	103.47 (97.16-110.19)	NA	100.59 (94.22-107.40)	NA
CV (%)	13.0	NA	13.6	NA

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

*ln-transformed values

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test and reference products in both studies.

As the additional 15 mg strength of rivaroxaban meets the biowaiver criteria specified in current guidance, the results and conclusions from the two bioequivalence studies on the 10 mg and 20 mg product strengths can be extrapolated to the 15 mg strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required.

IV.4 Clinical Efficacy

No new efficacy data were submitted and none were required.

IV.5 Clinical Safety

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 products are equally well tolerated. No new or unexpected safety issues were raised from these studies.

Risk Management Plan

Routine pharmacovigilance is considered sufficient and no additional pharmacovigilance activities are proposed. Additional risk minimisation measures include educational materials including the prescriber guide and patient alert card.

The schedule for Periodic Safety Update Reports (PSUR) submission should be addressed in accordance with the requirements set out in the list of Union reference dates (EURD list).

IV.6 Discussion on the clinical aspects

Data from the two clinical bioequivalence studies (for 10 mg and 20 mg strength) and the biowaiver request for the third 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 10 mg, 15 mg, and 20 mg film-coated tablets by Renata Pharmaceutical (Ireland) Ltd are generic forms of Xarelto, 10 mg, 15 mg & 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 10 mg, 15 mg, and 20 mg film-coated tablets by Renata Pharmaceutical (Ireland) Ltd demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted marketing authorisations to all three product strengths.

VI. REVISION DATE

20.10.2028