IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Rivaroxaban Ascend 15 mg film-coated tablets
Rivaroxaban
PA23429/007/003

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation on 29th August 2025 for Rivaroxaban Ascend 2.5 mg, 10 mg, 15 mg, 20mg and 15 mg + 20 mg film-coated tablets, from Ascend GmbH for the following indications.

2.5 mg film-coated tablets:

- the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine.
- 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, when co-administered with acetylsalicylic acid.

10 mg film-coated tablets:

- the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.
- deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

15 mg film-coated tablets:

Adults

- the 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.
- deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population

- 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

- the 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.
- deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population

- 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.

15 mg + 20 mg film-coated tablets:

- deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

With Ireland as the reference member state in this decentralised procedure, Ascend GmbH applied for marketing authorisations for Rivaroxaban Ascend 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets. There were three concerned member states involved in the procedure, Germany, Latvia and The Netherlands. The application was a generic application made according to Article 10(1) of Directive 2001/83/EC.

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

The originator product is Xarelto, 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets, registered centrally since 30 September 2008. The marketing authorisation holder is Bayer AG, 51368 Leverkusen, Germany.

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

The Summary of Product Characteristics (SmPC) for these medicinal products are available on the HPRA's website at www.hpra.ie

Name of the product	Rivaroxaban Ascend 15 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Rivaroxaban
Pharmacotherapeutic classification (ATC code)	B01AF01
Pharmaceutical form and strength(s)	film-coated tablets: 15 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA23429/007/003
Marketing Authorisation Holder	Ascend GmbH
MRP/DCP No.	IE/H/1281/003/DC
Reference Member State	Ireland
Concerned Member State	Germany, Latvia and The Netherlands

II. QUALITY ASPECTS

II.1. Introduction

This application is for Rivaroxaban Ascend 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets.

II.2 Drug substance

The active substance is Rivaroxaban Ph. Eur., an established active substance described in the European Pharmacopoeia. The active substance 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 have been provided.

II.3 Medicinal product

P.1 Composition

For each medicinal product:
The composition is stated in section 2 of the SmPC.
The excipients are listed in section 6.1 of the SmPC.
A visual description of the medicinal 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 tablets 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(s) 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 have been provided, assuring consistent quality of Rivaroxaban Ascend 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Xarelto, 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets and has been available on the European/Irish market for more than 10 years. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of Rivaroxaban are well known.

III.2 Ecotoxicity/environmental risk assessment

Since Rivaroxaban Ascend 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

The pharmacodynamic, pharmacokinetic and toxicological properties of Rivaroxaban are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. 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 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20mg film-coated tablets marketed by Bayer AG. For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Rivaroxaban Ascend 10 mg and 20 mg film coated tablets is compared with the pharmacokinetic profile of the reference product Xarelto (rivaroxaban) 10 mg and 20 mg film-coated tablets, respectively.

A biowaiver was sought for Rivaroxaban 2.5 mg and 15 mg film coated tablets. In line with the EMA's Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98/Rev. 1/Corr**), the criteria for a biowaiver are met.

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

IV.2 Pharmacokinetics

In support of this application, the applicant has submitted two bioequivalence studies.

The number and type of clinical studies in this application is in line with the rivaroxaban product-specific guidance (EMA/CHMP/160650/2016) in which it is stated that a fasting study should be conducted for the lower strengths and a fed study for the higher strengths, as there is a different food effect resulting in different food recommendations for the lower (2.5 mg and 10 mg) and the higher (15 mg and 20 mg) strengths. Submitted studies were conducted in accordance with the EMA's Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) for immediate release formulations with systemic actions.

Study 1: a fasting, oral bioequivalence study between Rivaroxaban Ascend 10 mg film-coated tablets (test) and Xarelto 10 mg film-coated tablets (reference) in healthy, adult, human subjects, and
Study 2: a fed, oral bioequivalence study between Rivaroxaban Ascend 20 mg film-coated tablets (test) and Xarelto 20 mg film-coated tablets (reference) in healthy, adult, human subjects.
A biowaiver has been requested for Rivaroxaban Ascend 2.5 mg and 15 mg film-coated tablets.

Results Study 1:
Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of rivaroxaban under **fasted** conditions

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1677.174 ± 321.6586	1711.612 ± 322.2323	204.793 ± 45.6549	2.667 (1.000 – 4.483)
Reference	1696.324 ± 399.4322	1722.600 ± 395.3285	206.259 ± 56.3456	2.175 (1.000 – 4.333)
* Ratio (90% CI)	99.8 (95.64 – 104.09)	100.2 (96.11 – 104.49)	100.6 (92.38 – 109.51)	-

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 C_{max} is reached

* ln-transformed values

Results Study 2:
Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of rivaroxaban under **fed** conditions

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	3548.909 ± 734.6443	3598.886 ± 730.5525	448.365 ± 85.0928	4.834 (1.017 – 6.000)
Reference	3767.654 ± 798.0415	3794.609 ± 799.3812	473.052 ± 84.2442	4.834 (1.333 – 5.500)
* Ratio (90% CI)	94.2 (91.19 – 97.35)	94.9 (92.10 – 97.84)	94.6 (89.66 – 99.77)	-

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 C_{max} is reached

* ln-transformed values

Conclusion on bioequivalence studies:
In accordance with the regulatory requirements for AUC_{0-t} and C_{max}, the 90 % confidence interval for the ratio of both strengths of the test and reference products falls within the conventional acceptance range of 80.00-125.00 %. Therefore, it can be concluded that the test product Rivaroxaban Ascend 10 mg film coated tablets is bioequivalent to the reference product Xarelto 10 mg film coated tablets under fasting conditions and that the test product Rivaroxaban Ascend 20 mg film coated tablets is bioequivalent to the reference product Xarelto 20 mg film coated tablets under fed conditions.

As the additional 2.5 mg and 15 mg strengths of rivaroxaban Ascend meet the biowaiver criteria specified in current guidance, the results and conclusions from the bioequivalence studies can be extrapolated to the 2.5 mg and 15 mg strengths.

IV.3 Pharmacodynamics

The pharmacodynamics of rivaroxaban are well established and adequately discussed in the clinical overview.

IV.4 Clinical Efficacy

No efficacy studies have been submitted and this is acceptable in keeping with the legal basis of this application.

IV.5 Clinical Safety

No new clinical safety studies have been submitted; this is acceptable in keeping with the legal basis 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 arise from these studies.

The SmPC captures the known relevant safety information.

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 Ascend.

Summary of safety concerns
The safety concerns of Rivaroxaban Ascend are aligned with those of the reference product (Xarelto - Risk management plan version 14.3 dated 24 Aug 2023) and are endorsed.

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 prosthetic heart valve

Pharmacovigilance Plan
The applicant proposes specific adverse reaction follow up questionnaires for the following AEs under routine pharmacovigilance activities:

- Liver-related adverse events
- Renal impairment/renal failure

No additional pharmacovigilance activities are proposed, which is endorsed.

Risk minimisation measures

Beyond routine risk minimisation measures (including safety messages in the SmPC and PL, Limited package supply and Prescription status), the applicant proposes additional risk minimisation measures with respect to the safety concern "Haemorrhage".

Educational material for prescribers and Patient alert card for patients are proposed, with the aim to increase awareness among prescribers/patients and reduce the risk of bleeding events.

The submitted RMP, version 0.4 dated 31 May 2025, is considered acceptable.

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 two clinical bioequivalence studies (for the 10 mg and 20 mg strengths) and the biowaiver request for the other two strengths (2.5 mg and 15 mg) have satisfactorily demonstrated bioequivalence between the test products of the applicant and the reference medicinal products. The results and conclusions from the bioequivalence studies and biowaiver request can be extrapolated to the 15 mg + 20 mg treatment initiation pack.

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 Ascend 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets by Ascend GmbH are generic forms of Xarelto (rivaroxaban) 2.5 mg, 10 mg, 15 mg, 20 mg and 15mg + 20 mg film-coated tablets. 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 content of the SmPC approved during the decentralised procedure is in accordance with that accepted for 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 the data submitted considered that Rivaroxaban Ascend 10 mg and 20 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted marketing authorisations to all four product strengths, Rivaroxaban Ascend 2.5 mg, 10 mg, 15 mg and 20 mg and to the treatment initiation pack containing the 15 mg + 20 mg film-coated tablets.

VI. REVISION DATE

07.07.2030