IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Apixaban 2.5 mg film-coated tablets
Apixaban
PA22865/009/001

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, on 24th November 2023, a marketing authorisation for Apixaban 2.5 mg film-coated tablets and Apixaban 5 mg film-coated tablets, by Renata Pharmaceuticals (Ireland) Limited, for the following indications:

- Apixaban 2.5 mg film-coated tablets

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

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

- Apixaban 5 mg film-coated tablets

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

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

This application was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as an 'generic' application. With Ireland as the Reference Member State (RMS) in this decentralised procedure, Renata Pharmaceuticals (Ireland) Limited applied for marketing authorisations for Apixaban 2.5 mg film-coated tablets and Apixaban 5 mg film-coated tablets in Ireland and Malta. The reference products were Eliquis 2.5 mg Film Coated Tablets (EU/1/11/691/003) and Eliquis 5 mg Film Coated Tablets (EU/1/11/691/009), MAH: Bristol-Myers Squibb/Pfizer EEIG.

Apixaban is an orally active, direct, selective inhibitor of the coagulation factor Xa (FXa) that reversibly binds directly to the active site of FXa. It inhibits free and clot-bound factor Xa, and prothrombinase activity. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

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	Apixaban 2.5 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Apixaban
Pharmacotherapeutic classification (ATC code)	B01AF02
Pharmaceutical form and strength(s)	Film-coated tablet; 2.5 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/009/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1229/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Apixaban 2.5 mg film-coated tablets and Apixaban 5 mg film-coated tablets.

II.2 Drug substance

The active substance is Apixaban, an established active substance, not 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 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 a suitably qualified manufacturing site.

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)

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 have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 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.8 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 and Pharmaceutical 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 Apixaban 2.5 mg and 5 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Eliquis 2.5 mg and 5 mg film-coated tablets on the European market. 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.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Apixaban 2.5 mg and 5mg film-coated tablets are generic products, an increased exposure to the environment is not anticipated. Additional environmental risk assessment studies are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of apixiban are well known. As apixaban is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of generic application. Nonclinical sections of the SmPC are in line with the originator which is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Apixaban is a well-known active substance with established safety, efficacy, and tolerability.

With the exception of data from a single bioequivalence study (Study 025-21), no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is satisfactory.

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

IV.2 Pharmacokinetics

For this generic application, the applicant has submitted the results of one bioequivalence study in which the pharmacokinetic profile of the test product, Apixaban 5 mg film-coated tablets, is compared with the pharmacokinetic profile of the reference product, Eliquis 5 mg film-coated tablets.

Study 025-21 was a randomised, single-dose, two treatment, two period, crossover bioequivalence study comparing the test product (Apixaban 5 mg film-coated tablets) to the reference product (Eliquis 5 mg tablets) in healthy adult human subjects under fasting conditions.

In each study period, subjects were administered a single oral dose of either the test or reference product after an overnight fast of at least 10 hours. Blood samples were taken pre-dose and up to 48 hours post-dose, with a wash-out period of 10 days between the treatment periods.

A summary of pharmacokinetic results is presented below:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	90% Confidence Intervals (%)	CV (%)
Ln (C_{max}) (ng/ml)	92.97	87.38 – 98.91	14.18
Ln (AUC_{0-t}) (hr*ng/ml)	99.59	93.51 – 106.06	14.40

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 product and the reference product. Therefore, based on the pharmacokinetic parameters of the active substance, the reference tablet (Eliquis 5 mg tablets) and test tablet (Apixaban 5 mg film-coated tablets) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

As the additional strength (2.5 mg) of the product met the biowaiver criteria specified in the current bioequivalence guidelines, the results and conclusions from the bioequivalence study on the 5 mg strength can be extrapolated to the lower strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

No new efficacy data were submitted and none are required for an application of this type.

IV.5 Clinical Safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from this study.

Risk Management Plan
A risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, was submitted, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Apixaban 2.5 mg Film-coated Tablets and Apixaban 5 mg Film-coated Tablets.

The summary of safety concerns is as follows:

Important identified risks	• Bleeding
Important potential risks	• Liver injury • Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	• Use in patients with severe renal impairment

Routine pharmacovigilance activities are proposed by the applicant, which is endorsed.
Additional risk minimisation measures in the form of educational materials (prescriber guide and patient alert card) are considered necessary to minimise the risk of bleeding.

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.

V. OVERALL CONCLUSIONS

Apixaban 2.5 mg film-coated tablets and Apixaban 5 mg film-coated tablets are generic forms of Eliquis 2.5 mg Film Coated Tablets and Eliquis 5 mg Film Coated Tablets. Eliquis is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence for Apixaban 2.5 mg film-coated tablets and Apixaban 5 mg film-coated tablets has been shown to comply with CHMP guidance documents.

The SmPC, Patient Leaflet and labelling are satisfactory, in line with current guidelines and 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 the data submitted, considers that Apixaban 2.5 mg film-coated tablets and Apixaban 5 mg film-coated tablets are bioequivalent to the reference products and demonstrate a satisfactory risk/benefit profile. Marketing authorisations are, therefore, granted for both strengths.

VI. REVISION DATE

12.10.2028