IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Blovarak 2.5 mg film-coated tablets
Apixaban
PA0568/036/001

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.

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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 for Blovarak 2.5mg & 5mg Film-coated Tablets, from Les Laboratoires Servier, on 30th October 2026 for the following indications:

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

Proposed therapeutic indications for 2.5 mg and 5 mg strengths:

Adults
Prevention of stroke and systemic embolism in adult patients with non-valvular 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 (see section 4.4 for haemodynamically unstable PE patients).

Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

This application was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. With Ireland as the Reference Member State (RMS) in this decentralised procedure, Les Laboratoires Servier, applied for marketing authorisations for Blovarak 2.5mg & 5mg Film-coated Tablets in Ireland, Belgium, Bulgaria, Croatia, Greece, Italy, Luxembourg, Romania and Spain.

The reference medicinal product is Eliquis 5mg film-coated tablets from Bristol-Myers Squibb-Pfizer EEIG authorised in the Community since 18th May 2011.

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

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	Blovarak 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)	2.5mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA0568/036/001
Marketing Authorisation Holder	Les Laboratoires Servier
MRP/DCP No.	IE/H/1402/001/DC
Reference Member State	IE
Concerned Member State	BE BG EL ES HR IT LU RO

II. QUALITY ASPECTS

II.1. Introduction

This application is for Blovarak 2.5mg & 5mg Film-coated Tablets.

II.2 Drug substance

The active substance Apixaban is a well-known active substance 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 pharmacopeial 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 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 pharmacopeial monograph for Film coated 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.

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 Blovarak 2.5mg & 5mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Eliquis 5 mg film-coated tablet on the European market since 2011. No new preclinical data have been submitted. 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

The ERA stops in Phase I. A Phase II environmental assessment is not required as according to the Phase I decision tree, question 2a/b/c/d, possible environmental risks for apixaban have already been sufficiently assessed in the authorization procedure for the medicinal product Eliquis.
Apixaban is not expected to pose a risk to the environment.

A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of apixaban 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. Overview based on literature review was provided and is acceptable for this type of generic application.

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 Pivotal bioequivalence study (study PLM-P2-095) 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 the studies is satisfactory.

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Eliquis marketed by Bristol-Myers Squibb-Pfizer EEIG, with the exception regarding paediatric indication and posology. The paediatric indication has been restricted to ≥ 35kg as the provided syringe is not suitable for accurate dosing below 35kg. For paediatric patients weighing < 35 kg, alternative pharmaceutical forms are available.

IV.2 Pharmacokinetics

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

Study PLM-P2-095 was a single-centre, randomised, single-dose, laboratory-blinded, two-period, two-sequence crossover study conducted in healthy male and female volunteers under fasting conditions. The study compared the test product, Apixaban 5 mg film-coated tablets, with the reference product, Eliquis 5 mg tablets.

The 90% confidence intervals for the test/reference ratios of the primary pharmacokinetic parameters were within the predefined acceptance limits for bioequivalence. Accordingly, the test product (Apixaban 5 mg film-coated tablets) and the reference product (Eliquis 5 mg tablets) were demonstrated to be bioequivalent with respect to the rate and extent of absorption, in accordance with the relevant CHMP guideline on the investigation of bioequivalence.

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 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 Blovarak 2.5 mg & 5 mg film-coated tablets

Safety specification

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

Pharmacovigilance Plan:

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

Risk minimisation measures:

Additional risk minimisation measures in the form of educational materials (patient alert card) are considered necessary to minimise the risk of bleeding.

Periodic Safety Update Report (PSUR):

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 medicine's 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.

IV.6 Discussion on the clinical aspects

This active substance, apixaban, has been available on the European market for more than 10 years. Apixaban is a well-known active substance with established safety, efficacy, and tolerability.

Bioequivalence between Blovarak 5 mg film-coated tablets and Eliquis 5 mg film-coated tablets has been demonstrated in accordance with applicable EU bioequivalence requirements. Based on the submitted data, a biowaiver for the 2.5 mg strength is accepted.

Blovarak 2.5 mg and 5 mg film-coated tablets are prescription-only medicinal products in Ireland.

The paediatric indication has been restricted to ≥ 35kg as the provided syringe is not suitable for accurate dosing below 35kg. For paediatric patients weighing < 35 kg, alternative pharmaceutical forms are available.

V. OVERALL CONCLUSIONS

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

The content of the product information is in line with current guidelines and consistent with that of the reference product. The paediatric indication has been restricted to ≥ 35kg, as the provided syringe is not suitable for accurate dosing below 35kg. Posology is only provided for paediatric patients weighing ≥ 35 kg. For paediatric patients weighing < 35 kg, alternative pharmaceutical forms are available.

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 Blovarak 2.5 mg & 5mg Film-coated Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

30.07.2031