IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Apixaban Aristo 1.25 mg/ml oral suspension
Apixaban
PA1983/011/001

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 Apixaban Aristo 1.25 mg/ml oral suspension, from Aristo Pharma GmbH, on 6th July 2026 for the following indications;

Adults

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 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 weighing ≥ 35 kg (see section 4.2).

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, Aristo Pharma GmbH applied for marketing authorisations for Apixaban Aristo 1.25 mg/ml oral suspension in Ireland and Germany. 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 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 for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Apixaban Aristo 1.25 mg/ml oral suspension
Name(s) of the active substance(s) (INN)	Apixaban
Pharmacotherapeutic classification (ATC code)	B01AF02
Pharmaceutical form and strength(s)	1.25 mg/ml oral suspension
Marketing Authorisation Number(s) in Ireland (PA)	PA1983/011/001
Marketing Authorisation Holder	Aristo Pharma GmbH
MRP/DCP No.	IE/H/1302/001/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Apixaban Aristo 1.25 mg/ml oral suspension.

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 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 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 oral suspension, 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 Apixaban Aristo 1.25 mg/ml oral suspension.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance, apixaban, has been available on the European/Irish market for more than 10 years. The reference medicinal product is Eliquis 5mg film-coated tablets from Bristol-Myers Squibb-Pfizer. 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

Since Apixaban Oral Suspension 1.25 mg/ml is a generic product, it is not expected to lead to increased exposure in the environment. Further environmental risk assessment is not required.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties apixaban are well known. As apixaban is a widely used and well-known active substances 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 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 a single bioequivalence study (Study ARL/21/214), 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.

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 bioequivalence study in which the pharmacokinetic profile of the test product Apixaban Aristo 1.25 mg/ml oral suspension is compared with the pharmacokinetic profile of the reference product Eliquis® 5 mg film-coated tablets.

Study ARL/21/214 was a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study comparing the test product (Apixaban Aristo 1.25 mg/ml oral suspension) to the reference product (Eliquis 5 mg tablets) in healthy adult human subjects under fasting conditions.

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 (Eliquis 5 mg tablets) and test (Apixaban Aristo 1.25 mg/ml oral suspension) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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.

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 1.25 mg/ml oral suspension.

The summary of safety concerns is as follows:

Summary of safety concerns	
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 (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.

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.

Apixaban Aristo 1.25 mg/ml oral suspension has been shown to be bioequivalent with Eliquis 5mg film-coated tablets, in compliance with the CHMP guidance documents.

Apixaban Aristo 1.25 mg/ml oral suspension is a prescription-only medicinal product 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

Apixaban Aristo 1.25 mg/ml oral suspension is a 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 Apixaban Aristo 1.25 mg/ml oral suspension demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

05.05.2031