IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Apixaban Abdi 2.5 mg film-coated tablet
Apixaban
PA23405/002/001

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 a marketing authorisation for Apixaban Abdi 2.5mg & 5mg Film-coated Tablets, from Abdi Farma GmbH, on Date of first authorisation: 15th November 2024 for the following indications:

Proposed therapeutic indications 2.5 mg strength
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.

This decentralised application concerns a generic version of apixaban, under Apixaban Abdi trade name, and is being submitted as a generic application under Article 10(1) of Directive 2001/83/EC as amended. Ireland is the reference member state, with Czechia, Germany, Hungary, Italy and Netherlands as concerned member states.

The legal status in Ireland is subject to medical prescription which may be renewed.

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 Abdi 2.5mg 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)	PA23405/002/001
Marketing Authorisation Holder	Abdi Farma GmbH
MRP/DCP No.	IE/H/1257/001/DC
Reference Member State	IE
Concerned Member State	CZ, DE, HR, IT, NL

II. QUALITY ASPECTS

II.1. Introduction
This application is for Apixaban Abdi 2.5mg & 5mg Film-coated Tablets

II.2 Drug substance
The drug substance Apixaban is a well-known active substance 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 and 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 suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and 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 relevant Ph. Eur. requirements and 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 Abdi film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Eliquis (2.5mg and 5mg, film-coated tablets) on the European market. No new preclinical data have been submitted. The applicant has not provided additional studies and further studies are not required. A nonclinical overview based on literature review was provided. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Apixaban Abdi is intended for generic substitution, this will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not deemed necessary.

III.3 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. 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 efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Eliquis.

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

This study was a randomised, open label, balanced, two treatment, two period, two sequence, single dose, crossover, BE study, in normal, healthy, adult, human subjects under fasting conditions. This was conducted to assess the BE of test and reference formulations. The wash out period between treatments was 7 days, which is deemed adequate given the half-life of approximately 12 hours for apixaban.

Bioequivalence was determined by a statistical comparison of Cmax and AUC0-t for the test and reference products for apixaban.

The test and reference products are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver of strengths was requested for the 2.5 mg strength. The requirements of the 'Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr. **' for a biowaiver of strengths are met.

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

IV.2 Pharmacokinetics

The pharmacokinetic bioequivalence study was a randomised, open label, balanced, two treatment, two period, two sequence, single dose, crossover, BE study, in normal, healthy, adult, human subjects under fasting conditions. This was conducted to assess the BE of test and reference formulations. The wash out period between treatments was 7 days, which is deemed adequate given the half-life of approximately 12 hours for apixaban.

Bioequivalence was determined by a statistical comparison of Cmax and AUC0-t for the test and reference products for apixaban. The key PK results are as follows:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC0-t ng/ml/h	AUC0-∞ ng/ml/h	Cmax ng/ml	tmax h
Test	1559.576 ± 318.900	1622.105 ± 308.978	170.707 ± 31.451	3.250 (1.000 – 4.500)
Reference	1618.564 ± 308.355	1673.325 ± 300.023	181.244 ± 26.951	3.500 (1.000 – 4.500)
*Ratio (90% CI)	96.1407 (92.6696 – 99.7418)		93.5441 (89.2901 – 98.0007)	

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC0-72h can be reported instead of AUC0-t, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
AUC0-∞ Area under the plasma concentration curve extrapolated to infinite time.
AUC0-∞ does not need to be reported when AUC0-72h is reported instead of AUC0-t
Cmax Maximum plasma concentration
tmax Time until Cmax is reached

*ln-transformed values

For AUC0-t and Cmax the 90% confidence interval for the ratio of the test and reference products falls within the conventional acceptance range of 80.00-125.00%. Therefore, we can conclude that bioequivalence has been demonstrated for the test and reference product at the 5mg strength. The results of this study with the 5mg formulation can also be extrapolated to the

2.5mg strength according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics
No new studies were performed or required for this Article 10(1) generic application.

IV.4 Clinical Efficacy
No new studies were performed or required for this Article 10(1) generic application.

IV.5 Clinical Safety
As the active substance is a widely used, well-known substance, the applicant has not provided additional safety studies and further studies are not required.

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 Apixaban Abdi 2.5mg & 5mg Film-coated tablets.

Safety specification

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

Pharmacovigilance Plan:

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

Risk minimisation measures:

Additional risk minimisation measures in the form of educational materials (prescriber guide and patient alert card) are in place minimise the risk of bleeding.

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 medicines 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

Discussion of clinical aspects has been provided in IV.1 – IV.6 above.

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

08.10.2029