COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Apixaban Macleods 2.5 mg and 5 mg film-coated tablets (apixaban)

NL/H/5518/001-002/DC

Date: 6 August 2024

This module reflects the scientific discussion for the approval of Apixaban Macleods 2.5 mg and 5 mg film-coated tablets. The procedure was finalised on 10 April 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apixaban Macleods 2.5 mg and 5 mg film-coated tablets from Macleods Pharma España S.L.U.

Apixaban Macleods has the following indications at different strengths:

Apixaban Macleods 2.5 mg
The product is indicated for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Apixaban Macleods 2.5 mg and 5 mg
The product is indicated for 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 heartfailure (NYHA Class ≥ II).

The product is indicated for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Eliquis 2.5 mg and 5 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/11/691) since 18 May 2011 by Bristol-Myers Squibb Pharma EEIG.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Apixaban Macleods 2.5 mg and 5 mg are film-coated tablets. Each film-coated tablet contains as active substance 2.5 mg or 5 mg apixaban. The two strengths of the film-coated tablets can be distinguished by the colours and debossing and are as follows:

Apixaban Macleods 2.5 mg
The 2.5 mg strength tablets are yellow, coloured, round, biconvex, film-coated tablets, debossed "F 51" on one side and plain on other side.

Apixaban Macleods 5 mg
The 5 mg strength tablets are pink, coloured, capsule shaped, film-coated tablets, debossed "F 52" on one side and plain on other side.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, sodium lauryl sulfate, povidone, and magnesium stearate (E572).
Film-coat - hypromellose (E464), triacetin (E1518), titanium dioxide (E171), and iron oxide yellow (E172; only for 5 mg strength) or iron oxide red (E172; only for 5 mg strength).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in polyvinyl chloride/polyvinylidene chloride-aluminium (PVC/PVdC-Al) blisters in cartons.

II.2 Drug Substance

The active substance is apixaban, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder, practically insoluble in water. For this product, polymorphic form I is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of a five step synthesis with two isolated intermediates. No class 1 organic solvents or heavy metal catalysts are used. Adequate specifications have

been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification has been established in-house by the applicant and is in line with the specification from the ASMF holder. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for four production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. The main development studies performed were the characterisation of the reference products, formulation optimisation studies, manufacturing process development studies, dissolution method development and the performance of comparative dissolution studies. The choice of the Quality Control dissolution method is justified and the discriminatory power of the method has been demonstrated. A bioequivalence (BE) study was performed with the 5 mg product strength. For the 2.5 mg product a biowaiver is shown. Comparative dissolution testing at 3 pHs has been successfully studied in support of the BE study and biowaiver.

Manufacturing process
The main steps of the manufacturing process are dry mixing of the intragranular components, wet granulation, mixing with extragranular components, lubrication, compression, film-coating and packaging.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. requirements with additional functionality-related characteristic or with in-house specifications (film-coating materials). These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, identification of colorants, loss on drying, dissolution, uniformity of dosage units, related substances, assay,

residual solvents (isopropyl alcohol) and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches per strength from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches per strength stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 5 years. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. No other substances are of ruminant animal origin

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Apixaban Macleods has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Eliquis which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Apixaban is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Apixaban Macleods 5 mg film-coated tablets (Macleods Pharma Espana S.L.U., Spain) was compared with the pharmacokinetic profile of the reference product Eliquis 5 mg, film-coated tablets (Bristol-Myers Squibb Pharma EEIG, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula for marketing.

<u>Biowaiver</u>
For the 2.5 mg strength, a biowaiver was granted because the following requirements were met, in accordance with the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all

strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21 to 41 years. Each subject received a single dose (5 mg) of one of the two apixaban formulations. The tablet was orally administered with 240 mL water after at least 10 hours fasting. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 1, 1.50, 2, 2.33, 2.67, 3, 3.25, 3.50, 3.75, 4, 4.33, 4.67, 5, 5.50, 6, 8, 12, 18, 24, 30, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Apixaban may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of apixaban. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrawn from the study in period I (post-dose) on principal investigator advice due to an adverse event (bleeding in eye). 23 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of apixaban, 5 mg under fasted conditions.

Treatment N=23	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	1576.49± 322.75	1590.91± 325.17	170.99± 31.65	3.00 (1.00-4.67)
Reference	1492.87± 406.58	1510.39± 409.96	155.72± 37.81	3.25 (1.00-4.67)
***Ratio (90% CI)**	1.08 (1.03-1.13)	-	1.12 (1.05-1.20)	

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Apixaban Macleods 5 mg is considered bioequivalent with Eliquis 5 mg.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Apixaban Macleods.

Table 2. Summary table of safety concerns as approved in RMP

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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Eliquis. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Apixaban Macleods 2.5 mg and 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Eliquis 2.5 mg and 5 mg, film-coated tablets. Eliquis is a well-known medicinal product with an established favourable efficacy and safety profile.
Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.
There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Apixaban Macleods with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 April 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-