COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Apixaban Pharmaplot MFN 1 mg/ml, oral suspension (apixaban)

NL/H/6207/001/DC

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This module reflects the scientific discussion for the approval of Apixaban Pharmaplot MFN 1 mg/ml, oral suspension. The procedure was finalised on 13 January 2026. 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
DVT	Deep Vein Thrombosis
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
NVAF	Non-Valvular Atrial Fibrillation
PE	Pulmonary Embolism
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
TSE	Transmissible Spongiform Encephalopathy
VTE	Venous Thromboembolism/Venous Thromboembolic Events

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apixaban Pharmaplot MFN 1 mg/ml, oral suspension, from Pharmaplot MFN P.C.

The product is indicated for:
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.

Paediatric population

- Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients weighing ≥ 35 kg.

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

In this decentralised procedure, therapeutic equivalence is proven between the new product and the innovator product Eliquis 5 mg film-coated tablets, which have been registered by Bristol-Myers Squibb/Pfizer EEIG in the EEA in 2011 via a centralised procedure (EU/1/11/691).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application. In a hybrid application there are specific differences between the product and its reference product. In this procedure, the product has differences in pharmaceutical form (oral suspension instead of film-coated tablets), strength (depending on the dosing) and therapeutic indication. Eliquis 5 mg has no VTE indication for adults. However, the therapeutic indications for the product are in line with the Eliquis 2.5 mg film-coated tablets. As Apixaban Pharmaplot MFN 1 mg/ml concerns a multidose preparation instead of a single dose preparation, the product can be used for dosing of both the 2.5 mg and 5 mg strength. Further, Eliquis 0.5 mg, 1.5 mg and 2 mg coated granules in sachets and Eliquis 0.15 mg granules in capsules have been registered in 2024 via a line-extension (NL License RVG 132018 and RVG 132023 – 132025). Both granule products have an indication for the paediatric population.
The weight restriction in the indication for paediatric patients, which is not present in the indication of the reference product, is included because the syringe in this specific product is not suitable for small children.

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

II. QUALITY ASPECTS

II.1 Introduction

Apixaban Pharmaplot MFN is an oral suspension. The suspension is off white to white and slightly viscous, with cherry flavour and a characteristic cherry odour. The pH range is between 3.5-4.5. Each ml of suspension contains as active substance 1 mg apixaban.

The excipients are: citric acid (E330), sodium citrate (E332), glycerol (E442), cherry flavour (1221/21) (containing propylene glycol), polysorbate 80 (E443), simethicone emulsion (containing polydimethylsiloxane, silica, methylcellulose and sorbic acid), sodium benzoate (E211), sucralose (E995), xanthan gum (E415) and purified water.

The oral suspension is filled in Ph. Eur. Type III dark amber glass bottles of 200 ml nominal volume, containing 150 ml of product, with plastic screw cap for children safety and a 10-ml dosing pipette with graduation of 0.5 ml for oral administration.

II.2 Drug Substance

The active substance is apixaban, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to yellow crystalline powder, practically insoluble in aqueous systems. Due to its non-ionisable nature, apixaban exhibits a pH – independent solubility profile. It is soluble in dimethylsulfoxide. Apixaban shows polymorphism and is consistently manufactured having the same polymorphic form, in the same polymorphic form as used in the reference product.

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 starts with the manufacturing of an intermediate, described in three synthetic steps/stages. The synthesis of the final substance is described in four steps of three chemical transformations and a final purification. No class 1 solvents nor heavy metal catalysts are used in the process. Micronisation may be performed upon customer requirement. 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 MAH and is based on the specification of the active substance manufacturer. 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 three production scale batches in accordance with applicable European guidelines demonstrating. Based on the data submitted, a retest period of 24 months is justified for the un-micronised active substance, 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 choice of excipients is justified and their functions are explained. The main development studies were the characterisation of the reference products, dissolution method development, excipient compatibility studies, formulation optimisation studies, stability of the particle size distribution, recovery studies to support administration of the drug product through a nasogastric tube and manufacturing process development studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of the preparation of a suspending vehicle where a buffer pre-mix, preservative premix and active substance premix is added to. The final suspension is sieved and filled in the designated containers. 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 in accordance with the relevant European guidelines.

Control of excipients

The excipients, except for the flavour agent and simethicone emulsion, comply with Ph.Eur. requirements. These specifications are acceptable. Since no Ph.Eur. monograph is available for simethicone emulsion, control according to the United States Pharmacopeia (USP) is acceptable. The in-house specification for cherry flavour is also acceptable.

Container closure system

Detailed information has been provided on the primary packaging material, including the specifications of the materials used, technical drawings and certificates of analysis. The glass bottle complies with Ph.Eur. Compliance with EU/10/2011 is confirmed for the dosing pipette, press in bottle adaptor and plastic screw caps. The child resistant claim of the closure is supported by a certificate, confirming that the screw caps comply with the current standards.

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 appearance, fill volume, pH, viscosity, uniformity of mass of the delivered dose, uniformity of dosage units, identification of apixaban and sodium benzoate, assay of apixaban and sodium benzoate, related substances, dissolution and microbiological quality. 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. Omission of nitrosamines control in the active substance is justified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site for three commercial scaled batches have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months) and 40°C/75% RH (6 months). The stability was tested 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 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the container.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Apixaban Pharmaplot MFN 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 Pharmacology, pharmacokinetics and toxicology

The pharmacodynamic, pharmacokinetic and toxicological properties of apixaban are well known. As apixaban is a widely used, well-known active substance, no further studies are required and the MAH provides none. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Apixaban Pharmaplot MFN is intended for hybrid substitution it will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

This product is a hybrid 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. Therefore, the member states agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study (23-VIN-0296) in which the pharmacokinetic profile of the test product Apixaban Pharmaplot MFN 1 mg/ml, oral suspension (Pharmaplot MFN P.C., Greece) was compared with the pharmacokinetic profile of the reference product Eliquis 5 mg film-coated tablets (Bristol-Myers Squibb/Pfizer EEIG, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Similarity between the dissolution profiles of test and reference could not be demonstrated. Bioequivalence was demonstrated *in vivo* and these results prevail, therefore test and reference product are considered bioequivalent. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover oral comparative bioavailability study was carried out under fasting conditions in 30 healthy male (26) / female (4) subjects, aged 20-44 years. Each subject received a single dose (5 mg) of one of the two apixaban formulations. The oral suspension or tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of nine days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 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

30 Subjects enrolled in the study. Five subjects did not report to the facility during period 2 admission, hence dropped out from the study. In total, 25 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=25	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	1211 ± 217	1231 ± 218	145 ± 30	2.00 (0.50-4.50)
Reference	1188 ± 246	1207 ± 248	124 ± 28	3.33 (1.00 – 4.52)
***Ratio (90% CI)**	1.03 (0.98 – 1.08)	--	1.15 (1.08 – 1.23)	--

$AUC_{0-\infty}$	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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Apixaban Pharmaplot MFN 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 Pharmaplot MFN. At the time of approval, the most recent version of the RMP was version 0.3 dated 14 November 2025.

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, besides routine pharmacovigilance activities and routine risk minimisation measures, the following additional risk minimisation measures must be taken by the MAH, in line with the reference product:

The MAH shall ensure that in each Member State where apixaban is marketed, all healthcare professionals who are expected to prescribe apixaban have access to/are provided with the following educational material:

- Summary of Product Characteristics
- Patient Cards

All patients and/or caregivers of paediatric patients who receive apixaban shall be provided with a Patient Card (provided within each medicine pack).

Key Elements of the Patient Card:

- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- Necessity to carry the patient alert card with them at all times
- The need to inform health care professionals that they are taking apixaban if they need to have any surgery or invasive procedure

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Eliquis. 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 hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Eliquis 5 mg film coated tablets, procedure number EMEA/H/C/2148. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Apixaban Pharmaplot MFN 1 mg/ml, oral suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Eliquis 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 Pharmaplot MFN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 January 2026.

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
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.