COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Prepixan 2.5 mg and 5 mg film-coated tablets (apixaban)

NL/H/6076/001-002/DC

Date: 1 April 2026

This module reflects the scientific discussion for the approval of Prepixan 2.5 mg and 5 mg film-coated tablets. The procedure was finalised on 2 October 2025. 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 Prepixan 2.5 mg and 5 mg film-coated tablets, from Vianex S.A.

Prepixan has the following indications at different strengths:

Prepixan 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.

Prepixan 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 heart failure (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.

Paediatric population
The product is indicated for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

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/Pfizer EEIG.

The concerned member state (CMS) involved in this procedure was Greece.

II. QUALITY ASPECTS

II.1 Introduction

Prepixan 2.5 mg and 5 mg are film-coated tablets. Each film-coated tablet contains 2.5 mg or 5 mg apixaban as active substance. The two strengths of the film-coated tablets can be distinguished by colour, size, shape, and debossing and are as follows:

Prepixan 2.5 mg
Yellow, round tablets (diameter of 6.1 mm and thickness of 2.8 – 3.2 mm), debossed with 2 ½ on one side.

Prepixan 5 mg
Pink, oval tablets (dimensions of 10.0 mm x 5.4 mm and thickness of 4.0 – 4.4 mm), debossed with 5 on one side.

The excipients are:
Tablet core – mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium, sodium laurilsulfate, and magnesium stearate (E470b).
Film coat – lactose monohydrate, hypromellose (E464), titanium dioxide (E171), polyethylene glycol (E1521), yellow iron oxide (E172; 2.5 mg only), and iron oxide red (E172; 5 mg only).

The two tablet strengths are dose proportional.

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

II.2 Drug Substance

The active substance is apixaban, an established active substance not yet described in any Pharmacopoeia (Ph.Eur.). The active substance is a white to pale yellow powder and is practically insoluble in water. For this product, one polymorphic form 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 synthesis of several chemical transformations from three starting materials. 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 (the drug substance specification match those of the drug substance manufacturer), with additional requirements for particle size distribution and microbial quality. The specification is acceptable.

Batch analytical data demonstrating compliance with this specification have been provided for three full-scale 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. Based on the stability data submitted, the claimed retest period is granted 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 and the levels of excipients are justified and their functions explained. Critical quality attributes (CQAs) were suitably defined and critical process parameters have been established during the process development.

An alternative administration for patients unable to swallow tablets suggests crushing and suspending them in 60 ml in total of the following liquids: water, 5% glucose (G5W) in water, apple juice and apple puree. If needed, the film coated tablets should be alternatively administered through an enteral feeding tube by crushing and dispersing the tablets in 60 ml water or G5W. Similar dissolution profiles of crushed tablets in water and G5W for both test and reference products for both strengths are achieved. Fast and complete dissolution profiles are observed in a study for all the test and reference products upon administration of the dispersed tables in water via an enteric tube. Based on the results it is observed that the drug substance passes uncomplicated through enteral tube supporting recovery of the initial dose.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements, except for the colouring agent which is manufactured by an established supplier and tested according to established methods. 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 appearance, identification, identification of colourants, average mass, uniformity of mass, disintegration, uniformity of dosage units, assay, dissolution, related substances and microbiological test. The specification limits have

been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided.

Satisfactory validation data for the analytical methods have been provided demonstrating the suitability of the employed methods.

Batch analytical data from three full-scale batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three production scaled batches stored at 25°C/65% RH, 30°C/65% RH, 30°C/75% RH and 40°C/75% RH for 12 months, in accordance with applicable European guidelines. Photostability studies were performed and showed that the product is stable when exposed to light. No changes over time were observed. 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 up to 4 hours in water, 5% glucose in water, apple juice and apple puree. The stability data shows that results of assay and related substances at 0 and 4 hours are compliant and the dissolution profiles of crushed tablets in all vehicles are comparable. The in-use stability of the product up to 4 hours in the mentioned vehicles is therefore accepted.

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 Prepixan 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 Prepixan 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 bioequivalence study, which is discussed below.
In addition to the bioequivalence study, a pilot study (Study VAX-P0-461) was carried out, to assess the pharmacokinetic performance of the test product and evaluate the comparability between the test and reference apixaban products in terms of the primary PK parameters. Another scope of this pilot study was to evaluate the intra-subject coefficient of variation and to define the terminal half-life (t½) of apixaban, in order to calculate the required sample size and determine an appropriate wash-out period, respectively, for the subsequent pivotal bioequivalence study.
The pilot study was carried out using the same study design and formulations as the bioequivalence study, under 12 healthy subjects.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Prepixan 5 mg film-coated tablets (Vianex S.A., 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. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements are met where the waiver for the 2.5 mg strength is claimed, according to 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 (at pH 1.2, 4.5 and 6.8) 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 study

Design

A single-dose, randomised, two-way, crossover bioequivalence study was carried out under fasted conditions in 24 healthy (12 male and 12 female) subjects, aged 19-59 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 a 10 hour overnight fast. Fasting was continued for 4 hours after dosing. There were two dosing periods, separated by a washout period of 7 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, 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

All 24 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=24	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1639 ± 292	1684 ± 298	178 ± 52	2.68 (1.00 – 8.00)
Reference	1717 ± 302	1753 ± 308	198 ± 48	2.68 (1.00 – 8.00)
***Ratio (90% CI)**	0.95 (0.91 – 1.00)	-	0.89 (0.84 – 0.94)	-

$AUC_{0-\infty}$	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 Prepixan 5 mg is considered bioequivalent with Eliquis 5 mg.

The results of the bioequivalence study with 5 mg formulation can be extrapolated to the 2.5 mg strength according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Prepixan. The most recent version of the RMP was version 1.0 dated 24 September 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

Routine risk minimisation measures as well as additional risk minimisation measures are in place; a prescriber guide and a patient card is included in relation to the safety concerns *bleeding* and a prescriber guide is included in relation to *Potential risk of bleeding or thrombosis due to overdose or underdose.*

Key messages of the additional risk minimisation measures

Physician educational material:

- The Summary of Product Characteristics
- Key Elements of the Prescriber Guide:
    - Details of populations potentially at higher risk of bleeding
    - Recommended dosages and guidance on the posology for different indications
    - Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
    - Guidance regarding switching from or to Prexipan treatment
    - Guidance regarding surgery or invasive procedure, and temporary discontinuation
    - Management of overdose situations and haemorrhage
    - The use of coagulation tests and their interpretation
    - That all patients should be provided with a Patient alert card and be counselled about:
        - 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 Prexipan if they need to have any surgery or invasive procedure.

- Key Elements of the Patient alert 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 Prexipan if they need to have any surgery or invasive procedure.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures as well as additional 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) for the 2.5 mg strength 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 Greek.

The test consisted of 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.

A user consultation with target patient groups on the package leaflet (PL) for the 5 mg strength has been performed on the basis of a bridging report making reference to Eliquis 5 mg film-coated tablets, EU/1/11/691 for content. Regarding the lay-out and design, a full user test was performed on the PL for Prexipan 2.5 mg, the PL for Prexipan 5 mg is similar in lay-out and design. 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

Prepixan 2.5 mg and 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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 Prexipan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 October 2025.

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
NL/H/6076/001-2/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/ hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	8-1-2026	Approved	N.A.