Medicines Evaluation Board

Public Assessment Report
Scientific discussion

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

NL/H/6100/001-002/DC

Date: 7 October 2026

This module reflects the scientific discussion for the approval of Apixaban Huahai 2.5 mg and 5 mg film-coated tablets. The procedure was finalised on 28 November 2025. For information on changes after this date, please refer to section 'steps taken after finalisation' at the end of this PAR.

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List of abbreviations

AE	Adverse Event
AI	Acceptable Intake
ANOVA	Analysis of Variance
BCS	Biopharmaceutics Classification System (-based biowaiver)
BE	Bioequivalence
CBG /MEB	College ter Beoordeling van Geneesmiddelen / The Medicines Evaluation Board
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(s)
DCP	Decentralised Procedure
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
ERP	European Reference Product
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IPC	In-Process Control
LALA	Locally applied, locally acting products
MAH	Marketing Authorisation Holder
NVAF	Non-Valvular Atrial Fibrillation
PAR	Public Assessment Report
PD	Pharmacodynamics
PE	Pulmonary Embolism
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PSURs	Periodic safety update reports
QC	Quality control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary
VTE	Venous Thromboembolic Events

Note: *Not all abbreviations may apply for this PAR.*

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apixaban Huahai 2.5 mg and 5 mg film-coated tablets, from Huahai Pharma Europe GmbH.

The products are indicated for:

2.5 mg strength only
Adults
Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

2.5 mg and 5 mg strengths
Adults
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 of the SmPC for haemodynamically unstable PE patients).

Paediatric population
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.

II. EXECUTIVE SUMMARY

II.1. Rationale for the product

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

To demonstrate bioequivalence with the reference medicinal product, the MAH has submitted data on a bioequivalence study for the 5 mg strength and has requested a biowaiver for the 2.5 mg strength. See Section V. Clinical aspects.

In this decentralised procedure the reference medicinal product is Eliquis 2.5 mg and 5 mg film-coated tablets, which has been authorised in the EEA via the centralised procedure EU/1/11/691 by Bristol-Myers Squibb / Pfizer EEIG since 18 May 2011. In the Netherlands, Eliquis has been authorised via procedure EMEA/H/C/002148 since 18 May 2011.

This application has been assessed with The Netherlands as Reference Member State (RMS) and Germany as concerned Member State (CMS).

II.2. About the product

Apixaban is a potent, direct, oral, reversible, and highly selective inhibitor of factor Xa. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

Pharmaco-therapeutic group (ATC Code): B01AF02
Dispensing status: Prescription-Only

II.3. General comments on the application

N.A.

II.4. General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the medicinal product and batch release situated in the EU.

GCP
Based on the data and documents submitted, the RMS has been assured that the study was conducted and reported in compliance with GCP: a GCP statement and audit certificate(s) were provided; monitoring report(s) and recent inspection(s) by competent authorities identified no concerns relevant to the study; and, where conducted outside the EU, compliance with the ethical requirements of EU legislation (Directive 2001/20/EC or Regulation EU No. 536/2014, as relevant) was confirmed

III. QUALITY ASPECTS

III.1. Introduction

Apixaban Huahai are film-coated tablets containing either 2.5 mg or 5 mg apixaban as active substance. The film-coated tablets of the different strengths can be distinguished by their colour, shape, and debossing and are as follows:

Apixaban Huahai 2.5 mg
Yellow, round, biconvex film-coated tablets debossed with '630' on one side and 'S' on the other side, with a diameter of approximately 6 mm.

Apixaban Huahai 5 mg
Pink, oval, biconvex film-coated tablets debossed with '631' on one side and 'S' on the other side, approximately 10 mm x 5 mm.

The excipients are:
Tablet core – lactose, microcrystalline cellulose, sodium laurilsulfate, croscarmellose sodium, and magnesium stearate.
Tablet coating – hypromellose, titanium dioxide (E171), talc (2.5 mg only), macrogol (2.5 mg only), iron oxide yellow (E172), lactose monohydrate (5 mg only), triacetin (5 mg only), iron oxide red (E172; 5 mg only), and iron oxide black (E172; 5 mg only).

The tablet strengths are dose proportional.

The film-coated tablets are packed in transparent polyvinyl chloride-polyvinylidene chloride/Aluminium (PVC-PVdC/Alu) blisters.

III.2. Active Substance

The structure of the active substance has been adequately proven and its physico-chemical properties are sufficiently described. The active substance is apixaban, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to yellow crystalline powder and insoluble in water.
Apixaban exhibits polymorphism, for this product, polymorphic form N-1 is consistently produced.

Manufacturing process
The manufacture of the active substance has been adequately described. The used starting materials, solvents and reagents are considered acceptable. Adequate tests and acceptable specifications have been adopted for these.

Quality control of the active substance
The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified in accordance with the applicable ICH Guidelines for impurities in new Drug Substances. The analytical methods applied are suitably described and non-compendial methods have adequately been validated. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches.

Stability of the active substance
Development studies have shown that the active substance is not sensitive to light.

Stability data have been submitted for three production scale batches and six pilot scale batches of the active substance in accordance with the applicable European guidelines. Based on the data submitted, the re-test period for the active substance was confirmed for 48 months when stored under the stated conditions. This is acceptable.

III.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 the excipients is justified, and their functions explained. Comparative dissolution testing at 3 pHs has been successfully studied in support of the bioequivalence study and biowaiver. The QC dissolution method is changed to a 50 rpm paddle speed (in the second round), which is according to the reflection paper.
According to the SmPC, patients who are unable to swallow whole tablets, Apixaban Huahai tablets may be crushed and suspended in water, or 5 % glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Apixaban Huahai tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube. The compatibility of the product with a nasogastric tube is shown adequately with 3 types of materials and the worst case of dimension.

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified. The manufacturing process has been validated according to relevant European/ICH guidelines.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the current version of the Ph.Eur. monograph or in-house requirements. These specifications are acceptable.

Quality control of the medicinal product
The medicinal product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, water content, identification (by two methods), dissolution, assay, impurities, uniformity of dosage units, identification of colouring agents and microbiological quality. The release and shelf-life tests and limits are identical are for all test parameters. The specification for shelf life has been adjusted to include all tests and a footnote for the tests not carried out during shelf life were added. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product.

An adequate risk evaluation report on nitrosamines has been submitted. No risk for the presence of nitrosamines in the medicinal product was identified. This justifies the absence of any further testing for nitrosamine impurity in the active substance and medicinal product.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data for three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of the medicinal product
Stability data on the product have been provided for three production scaled batches of each strength stored at 25°C/ 60% RH (18 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. The results showed that the product is stable when exposed to light. Based on the data submitted, a shelf life of 30 months was granted. The labelled storage conditions are: *'This medicinal product does not require any special storage condition'.*

Crushed Apixaban Huahai tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific TSE/BSE free certificates of suitability issued by the EDQM for anhydrous lactose 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

III.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member States consider that Apixaban Huahai has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and medicinal product.

IV. NON-CLINICAL ASPECTS

IV.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of apixaban are well known. As apixaban is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. The submitted overview based on literature is appropriate.

IV.2. Ecotoxicity/environmental risk assessment (ERA)

At the time of the approval of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. Then the conclusion for this medicinal product was: since Apixaban Huahai 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.

IV.3. 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 reference medicinal 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.

V. CLINICAL ASPECTS

V.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 discussed below. Bioequivalence has been investigated in line with the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

V.2. Pharmacokinetics

To support the application, the MAH has submitted one bioequivalence study comparing the pharmacokinetic profiles under fasted conditions of the test product Apixaban Huahai 5 mg film-coated tablets, Huahai Pharma Europe GmbH, Germany and the reference medicinal product Eliquis 5 mg film-coated tablets, Bristol-Myers Squibb/Pfizer EEIG, Germany. A biowaiver was requested for the lower strength **2.5 mg.** The formula and manufacturing process of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver
According to the EMA bioequivalence guideline, the following general requirements must be met where a waiver for additional strength is claimed:

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 MAH provided comparative dissolution profiles of the dose-proportional strengths of the test product (2.5 mg) at pH 1.2, 4.5 and 6.8. Comparative dissolution has been sufficiently demonstrated. 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.
As all the conditions for the biowaiver criteria are met, a biowaiver for the lowest strength 2.5 mg has been granted.

Bioequivalence study, study number 2809

Design
A single-dose, randomised, open label, two-treatment, two-period, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male (7) and (non-pregnant) female (17) subjects, aged 27-64 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

fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 9, 12, 16, 24, 48 and 60 hours after administration of the products.

The SmPC recommends administering the product orally, with or without food.

The design of the study was considered acceptable as according to the SmPC apixaban may be administered without reference to food intake. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH M10 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 of the subjects withdrew from the study due to unknown reason. A total of 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	1857 ± 592	1895 ± 590	197 ± 49	2.00 (1.00 – 5.00)
Reference	1898 ± 562	1932 ± 554	209 ± 49	2.50 (1.00 – 4.50)
***Ratio (90% CI)**	97.38 (93.69 – 101.22)	97.58 (94.35 – 100.93)	93.90 (88.75 – 99.36)	-

$AUC_{0-\infty}$	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 = 60 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Back-transformed from ln-transformed least-squares mean values

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the conventional bioequivalence acceptance range of 80% – 125%. Based on the submitted bioequivalence study Apixaban Huahai is considered bioequivalent with Eliquis 5 mg under fasted conditions.

As a biowaiver has been granted, the results of study 2809 with the 5 mg formulation can be extrapolated to the lower strength of 2.5 mg, in accordance with the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

V.3. Summary Pharmacovigilance system

The MAH has submitted a signed Summary of the MAH's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable

V.4. 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 Huahai. At the time of approval, the accepted version of the RMP was version 0.3 with sign-off date 20 October 2025.

Table 2. Summary table of safety concerns as approved in the 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 several renal impairment

Additional risk minimisation measures (including educational material) are considered necessary. See section *IX.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC*.
The Member States agreed that routine pharmacovigilance activities and the additional risk minimisation measures are sufficient for the risks and areas of missing information.

V.5. Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the reference medicinal 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 medicinal product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference medicinal product.

VI. 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report making reference to Eliquis 2.5 mg film-coated tablets, EMEA/H/C/002148 for key messages, and to Alunbrig 30 mg, 90 mg and 180 mg film-coated tablets, EMEA/696925/2018 for layout and design. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VII. POST-APPROVAL COMMITMENTS (PAC's)

N.A.

VIII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Apixaban Huahai 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 between the test and reference medicinal products, in line 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, based on the data submitted, considered that essential similarity has been demonstrated for Apixaban Huahai with the reference medicinal product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 November 2025.

IX. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

IX.1. List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N.A.

IX.2. List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

The following post-approval commitments apply:

- The MAH shall ensure that in each Member State where apixaban Huahai is marketed, all healthcare professionals who are expected to prescribe apixaban 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) containing the following key elements:

  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 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

- Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83.

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.