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Public Assessment Report

Scientific discussion

Cloter 2.5 mg film coated tablets
Cloter 5 mg film coated tablets
(apixaban)

ES/H/0956/001-002/DC

Date: 20/07/2026

This module reflects the scientific discussion for the approval of Cloter 2.5 mg, 5 mg film coated tablets. The procedure was finalised at 23 February 2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cloter 2.5 mg and 5 mg film coated tablets, from Laboratorios Alter S.A.

The product is indicated for*:*
Cloter 2.5 mg film coated tablets
-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 (see section 4.4 for haemodynamically unstable PE patients).

Cloter 5 mg film coated tablets
-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 for haemodynamically unstable PE patients).

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished products are presented as film coated tablets containing 5 mg and 2.5 mg of apixaban as active substance. The maximum daily dose is 20 mg.

Cloter 2.5 mg and 5 mg film coated tablets are packaged in PVC/PVdC aluminium blisters.

II.2 Drug Substance

The ASMF procedure is used to support the quality of the drug substance.

General Information

Nomenclature:

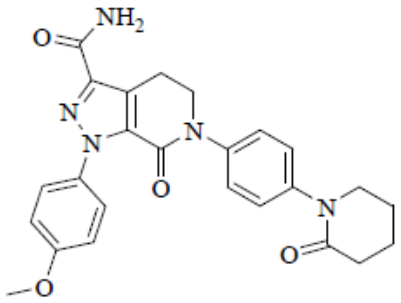
INN: Apixaban

Chemical name: 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

CAS-No: [503612-47-3]

Structure:

Structural formula:



Molecular formula: $C_{25}H_{25}N_5O_4$

Molecular weight: 459.50

General Properties:

Apixaban is a white to yellow crystalline powder, not hygroscopic. At 25°C, Apixaban is slightly soluble in methanol, practically insoluble in ethyl acetate and in water.

Manufacture, process controls and characterisation

The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

II.3 Medicinal Product

Description of the product

Cloter 2.5 mg film coated tablets are round, white, biconvex unscored film coated tablets (approximate 6 mm diameter).

Cloter 5 mg film coated tablets are oblong, white, biconvex unscored film coated tablets (approximate 13 mm x 5.3 mm).

The qualitative composition of the drug product is as follows:
Apixaban
Lactose
Microcrystalline cellulose
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate
Film coating:
Hypromellose
Titanium dioxide (E171)
Triacetin

The packaging material intended for the commercial use consists in PVC/PVdC aluminium blisters.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

Lactose is an excipient of animal origin. Scientific data and/or certificates are presented to guarantee compliance with the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents* for this excipient.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in PVC/PVdC aluminium blisters. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 3 years

Storage conditions: This medicinal product does not require any special storage condition.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

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. Overview based on literature review is, thus, appropriate.

III.2 Environmental risk assessment (ERA)

Since Cloter 2.5 mg and 5 mg film coated tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Apixaban is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted one bioequivalence study with the 5 mg strength according to the Guideline on the investigation of bioequivalence, which is discussed below.

IV.2 Pharmacokinetics

<u>Biowaiver</u>

The application concerns 2.5 mg and 5 mg film coated tablets.

A bioequivalence study was conducted for the 5 mg strength. A biowaiver is granted for the lower strength as all general requirements of the Guideline on the Investigation of Bioequivalence are met:

- The two strengths are manufactured with the same process.
- The qualitative composition of the two strengths is the same.
- The composition of the strengths is quantitatively proportional.
- Appropriate dissolution profiles between the different strengths have confirmed to be similar.

Bioequivalence study

Study code
UECHUP-API/23-1

GCP compliance
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical Study Site
Clinical Trials Unit, Hospital Universitario de la Princesa. C/ Diego de León, 62 28006, Madrid, Spain

Bioanalytical Study Site
Anapharm Europe, S.L.U. Encuny, n.22, 2nd floor 08038 Barcelona, Spain

Design
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 36 healthy volunteers under fasting conditions.
After an overnight fast of at least 8 hours one tablets of 5 mg of either test or reference was administered together with 240 ml of water. Fasting continued until approximately 5 hours after drug administration.
The study periods were separated by a wash-out period of 7 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence.
Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
36 subjects, were included in the study. 36 subjects were treated, 36 subjects completed the study and were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Summary of assessment bioequivalence studies.

Table 1. Pharmacokinetic parameters for Cloter and Eliquis (N=36) (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1578.87 ± 382.42	1616.26 ± 385.93	147.15 ± 36.85	3.25 (1.00-5.00)
Reference	1531.65 ± 346.43	1566.31 ± 346.57	145.29 ± 33.16	3.50 (1.00-5.00)
***Ratio (90% CI)**	**102.69 (98.60 -106.94)**	**102.77 (98.87-106.82)**	**100.79 (92.79-109.48)**	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

*ln-transformed values

Conclusion on bioequivalence study:

Based on the submitted bioequivalence study UECHUP-API/23-1, Cloter 5 mg film coated tablets is considered bioequivalent with Eliquis 5 mg film coated tablets.

The results of study UECHUP-API/23-1 with 5 mg formulation can be extrapolated to other strength 2.5 mg, 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/ Clinical efficacy/ Clinical safety

No original studies were submitted. This is acceptable in the context of a generic application, and no additional PD, efficacy or safety studies are deemed necessary. The efficacy and safety of apixaban have been demonstrated in several clinical trials conducted with the reference product and during post-marketing experience. Therapeutic indication proposed for Cloter 2.5 mg and 5 mg film coated tablets is the same as that authorized for the reference product, Eliquis® 2.5 and 5 mg film-coated tablets.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 0.4, 29 January 2025), 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 2.5 mg and 5 mg tablets.

- Summary table of safety concerns as approved in RMP

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	• Severe renal impairment

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
-Bleeding	- SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9. - PL sections 2 and 4. - Prescription only medicine.	-Prescriber Guide -Patient alert card.
Important Potential Risks		
-Liver injury	- SmPC sections 4.2, 4.3, 4.4 and 4.8. - PL sections 2 and 4. - Prescription only medicine.	-None
-Potential risk of bleeding or thrombosis due to overdose or underdose	- SmPC sections 4.2 and 4.9. - PL section 3. - Prescription only medicine.	-Prescriber Guide
Missing Information		
-Severe renal impairment	- SmPC sections 4.2, 4.4 and 5.2. - PL section 2. - Prescription only medicine.	-None

- Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the MAH.

IV.5 Discussion on the clinical aspects

Please refer to section IV.2.

V. USER CONSULTATION

In order to justify this bridging report, two different parent PILs have been used for Cloter 2.5 mg and 5 mg film coated tablets (Daughter PILs):

- Eliquis 2.5 mg film coated tablets and Eliquis 5 mg film coated tablets (Parent PILs-1) was used for text information (key safety messages).

- Couldina con Ibuprofeno comprimidos efervescentes (Parent PIL-2) was used for desing and layout.

Cloter 2.5 mg film coated tablets
The readability of the package leaflet of the product in this application (daughter PL) –Cloter 2.5 mg film coated tablets – is demonstrated by the comparison between the proposed package leaflet text and the leaflet texts of the parent PL –Eliquis 2.5 mg film-coated tablets (reference product)– for which was performed a readability test with acceptable results (EU/1/11/691/001-

019). The package leaflet for Cloter 2.5 mg film coated tablets- is basically identical except for product specific information and have no impact on the readability of the PIL.

Cloter 5 mg tablets
The readability of the package leaflet of the product in this application (daughter PL) –Cloter 5 mg film coated tablets – is demonstrated by the comparison between the proposed package leaflet text and the leaflet texts of the parent PL –Eliquis 5 mg film-coated tablets (reference product)– for which was performed a readability test with acceptable results (EU/1/11/691/001-019). The package leaflet for Cloter 5 mg film coated tablets- is basically identical except for product specific information and have no impact on the readability of the PIL.

For the design and layout, the Bridging Report is comparing the design and layout of the proposed package leaflets – Cloter 5 mg and 2.5 mg tablets – with the package leaflet of the product Couldina con Ibuprofeno comprimidos efervescentes tested by readability test with positive results. The design and layout of both products are similar (NAP registered number in Spain: 81.807).

Based on the above justification the daughter PIL is considered comparable with the parent PILs and assessed as readable in compliance with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Cloter is found adequate. There are no objections to the approval of Cloter 2.5 mg and 5 mg film coated tablets from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

The results of the study with the 5 mg strength 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.