COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/6093/001-002/DC

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This module reflects the scientific discussion for the approval of Apixaban TOWA Pharmaceutical 2.5 mg and 5 mg film-coated tablets. The procedure was finalised on 19 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
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 TOWA Pharmaceutical 2.5 mg and 5 mg film-coated tablets, from Towa Pharmaceutical Europe S.L.

The product is indicated for:

Adults

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery (only for the 2.5 mg strength).
- 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 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 since 18 May 2011 by Bristol-Meyers Squibb/Pfizer EEIG via a centralised procedure (EU/1/11/691).

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

II. QUALITY ASPECTS

II.1 Introduction

Apixaban TOWA Pharmaceutical are film-coated tablets. The two strengths are visually distinguishable by their colour, shape, size and debossing, as follows:

- The 2.5 mg strength is a yellow, round tablet (diameter of 6.1 mm) debossed with "E23" on one side and plain on the other side. Each tablet contains 2.5 mg of the active

substance apixaban.

- The 5 mg strength is a pink, oval tablet (10 mm x 5 mm) debossed with "E124" on one side and plain on the other side. Each tablet contains 5 mg of the active substance apixaban.

The excipients are (for both strengths):
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, sodium laurilsulfate, magnesium stearate (E470b) and copovidone.
Film coat - lactose monohydrate, hypromellose 2910 (E464), titanium dioxide (E171), triacetin, iron oxide red (E172), iron oxide yellow (E172, only the 5 mg strength) and iron oxide black (E172, only the 5 mg strength).

The tablet cores of the two strengths are dose proportional.

The film-coated tablets are packed in blisters made of polyvinyl chloride/polyvinylidene chloride-aluminium (PVC/PVdC-Al) or in high-density polyethylene (HDPE) bottles.

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 pale yellow crystalline powder, insoluble in water. Apixaban is consistently manufactured having the same polymorphic form.

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 five chemical transformation steps followed by purification. Adequate specifications have been adopted for starting materials, solvents and reagents. No class 1 solvents or heavy metal catalysts are used in the process. 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 in line with the specification of the active substance manufacturer, with additional requirements for particle size distribution. 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 four batches.

Stability of drug substance

Stability data on the active substance have been provided for several production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months 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 explained. The choices of the packaging and manufacturing process are justified. The main development studies were the characterisation of the reference products, dissolution method development, formulation optimisation studies and manufacturing process development studies. The choice of the QC dissolution method has been justified. The pharmaceutical development of the product has been adequately performed.

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 or 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. The feasibility to administer the product through a nasogastric tube has been adequately demonstrated under worst-case conditions (8 Fr tubes) and was shown to be comparable to the reference product.

Manufacturing process

The main steps of the manufacturing process are the preparation of an extrudate of apixaban, blending, tabletting, 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 at least three full scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. or in-house requirements. Their 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, average mass, water content, identification, dissolution, assay, degradation products, uniformity of dosage units, disintegration 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. 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 pilot scaled batches per 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 per strength stored at 25°C/ 60% RH (36 months), 30°C/75% RH (36 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 two years. No specific storage conditions needed to be included in the SmPC or on the label.

The stability of the product for up to 4 hours after suspending it in different vehicles has been demonstrated. Furthermore, tablets of both product strengths were crushed and suspended in water with 5% glucose, apple juice or applesauce for 4 hours and evaluated for degradation impurities. No degradation was seen. 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

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Apixaban TOWA Pharmaceutical 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 TOWA Pharmaceutical 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 one bioequivalence study, which is discussed below. In addition, a biowaiver on strengths was requested.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Apixaban TOWA Pharmaceutical 5 mg film-coated tablets (Towa Pharmaceutical Europe S.L., Spain) was compared with the pharmacokinetic profile of the reference product Eliquis 5 mg film-coated tablets (Bristol-Meyers 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 were met for a waiver for the additional lower 2.5 mg strength, 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 according to the EMA Bioequivalence guideline. Where applicable, 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 Study RP.16.1441

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover, pivotal bioequivalence study was carried out under fasted conditions in 26 healthy male (20) and female (6) subjects, aged 23-41 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 an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 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

26 Subjects enrolled in the study. One subject was withdrawn due to not showing up for Period II. 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_{0-48} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	1778 ± 430	1810 ± 438	186 ± 44	3.00 (0.67 - 5.00)
Reference	1836 ± 447	1863 ± 448	201 ± 44	3.50 (0.67 - 5.00)

***Ratio (90% CI)**	0.96 (0.92 – 1.01)	--	0.92 (0.88 – 0.96)	--

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

The results of study RP.16.1441 with the 5 mg formulation can be extrapolated to the lower 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 Apixaban TOWA Pharmaceutical. At the time of approval, the most recent version of the RMP was version 1 dated 24 December 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, for the safety concerns as mentioned in table 2, the following (additional) risks minimisation measures and pharmacovigilance activities must be taken by the MAH:

Table 3. Risk minimisation measures and pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities

Bleeding	**Routine risk minimisations measures:** SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9 **Additional risk minimisation measures:** • Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Post-marketing targeted bleeding questionnaire
Liver injury	**Routine risk minimisations measures:** SmPC sections 4.2, 4.3, 4.4 and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Post-marketing questionnaire for spontaneous reports of liver events
Potential risk of bleeding or thrombosis due to overdose or underdose	**Routine risk minimisations measures:** SmPC Sections 4.2 and 4.9	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None
Use in patients with severe renal impairment	**Routine risk minimisations measures:** SmPC provides the dosing recommendation for patients with severe renal impairment for each indication.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None

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 materials:

- 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 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 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.

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 2.5 mg film-coated tablets, procedure number EMEA/H/C/002148 for the key messages, and to Duloxetina NewLine Pharma 30 mg & 60 mg cápsulas duras gastrorresistentes, (Spanish AEMP registration numbers 79545 & 79546), for the design and layout. 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 TOWA Pharmaceutical 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. The product is considered suitable for administration via a nasogastric tube as suspended crushed tablets, in line with the option given for the reference product.

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 TOWA Pharmaceutical with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 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
-	-	-	-	-	-