LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Apixaban Glenmark
(apixaban)

SE/H/2563/001-002/DC

This module reflects the scientific discussion for the approval of Apixaban Glenmark. The procedure was finalised at 2026-01-21. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Apixaban Glenmark, 2,5 mg, 5 mg, Film-coated tablet.

The active substance is apixaban. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clotbound 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. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

II.2 General comments on the submitted dossier

The application for Apixaban Glenmark, 2,5 mg, 5 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, NL, DK, NO, FI, SK. AT, IT, CZ and ES as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Eliquis 2,5 mg and 5 mg film-coated tablets authorised in Union since 2011, with Bristol-Myers Squibb/Pfizer EEIG as marketing authorisation holder.

The reference product used in the bioequivalence studies is Eliquis 5 mg film-coated tablets from Germany with Bristol-Myers Squibb/Pfizer EEIG as marketing authorisation holder.

II.3 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.

GCP
A statement on the application of appropriate GCP standards in the submitted studies has been provided. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of Apixaban Glenmark are well known. As Apixaban Glenmark is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Phase I			
Calculations		**Results**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)		0.175 µg/L (refined F_{pen})	>0.01 µg/L threshold (Yes)
Other concerns (e.g. chemical class)		-	No
Phase II Physical-chemical properties and Fate			
Study Type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 12.2 L/kg	
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$: 31.5-41.7 d $DT_{50\ whole\ system}$: 100-182 d % shifting to sediment: 40.2-52.0	Determined at 20 °C Apixaban is persistent in sediments
Phase IIa Effect Studies			
Study Type	**Test protocol**	**Results**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC: 3600 µg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC: 9600 µg/L	*Daphnia sp.*
Fish, Early Life Stage Toxicity	OECD 210	NOEC: ≥10000 µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC: >100,000 µg/L EC_{50}: >100,000 µg/L	
Phase IIb Studies			
Study Type	**Test protocol**	**Results**	**Remarks**
Sediment dwelling organism	OECD 218	NOEC: ≥100 mg/kg_{dw} (organic carbon content of sediment 2.4%)	*Chironomus sp.*

PBT Assessment

The n-octanol/water partition coefficient of apixaban (log Kow: 1.17, 1.18 and 1.13 for pH 5.01, 7.0 and 9.01, respectively) [Study No. 20401/2025], was significantly below the threshold of 4.5, thus not

requiring further persistence, bioaccumulation and toxicity assessment [EMA-ERA, 2024].

Substance (INN/Invented Name): Apixaban			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential log K_{ow}	OECD 107	log K_{ow} 1.2	Not PBT/vPvB
PBT-Assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	Log K_{ow}	1.2	Not B
	BCF	Not triggered	
Persistence	Ready biodegradability	No readily biodegradable	Potentially persistent
	$DT_{50\ water}$	31.5-41.7 d at 20 ^{0}C	
	$DT_{50\ whole\ system}$	100-182 d at 20 ^{0}C	
Toxicity	NOEC or CMR	>1 mg/L, not CMR	Not T
PBT Statement : The compound is not considered as PBT not vPvB			

There are no objections to approval of Apixaban Glenmark from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Apixaban Glenmark, 5 mg, tablet, with the reference product Eliquis, 5 mg, film-coated tablet in both the fasted and the fed state.

Apixaban is an immediate-release formulation, which can be taken independent of meals. The product-specific bioequivalence guidance for Apixaban film-coated tablet 2.5 and 5 mg (EMA/CHMP/291499/2018) recommends a single-dose study in the fasted state. However, the applied formulation is considered a solid dispersion. According to ICH M13A Guideline on bioequivalence for immediate release solid oral dosage forms (EMA/CHMP/ICH/953493/2022), high-risk products, characterised by complex formulations and/or manufacturing processes (such as solid dispersions), may exhibit varying *in vivo* performance under different gastrointestinal conditions. For these products, both fasting and fed bioequivalence (BE) studies are required, as results from a single fasting BE study may not be extrapolated to predict fed BE study outcome. Initially, the applicant submitted only a study in the fasted state. However, in accordance with the day 70/100 comments, the applicant conducted, and submitted, a study in the fed state, to meet the applicable requirements and guidelines.

Pharmacokinetic properties of the active substance
Absorption: Apixaban has an oral bioavailability of 50 % for doses up to 10 mg. Following an oral dose of apixaban maximal plasma concentrations occur at approximately 3-4 hours.

The pharmacokinetics of apixaban is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of apixaban is linear within the dose range 2.5-10 mg.

Elimination: The terminal half-life is approximately 12 hours.

Study GRC – BS – 048 – 23, FASTING

Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Apixaban Glenmark, 5 mg, tablet, with Eliquis, 5 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of apixaban were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2024-05-06 and 2024-06-01.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for apixaban, n=48.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**1641.83 ± 272.23**	**174.28 ± 30.83**	**2.00 (0.75 – 4.50)**
Reference	**1493.16 ± 286.02**	**152.69 ± 29.77**	**3.00 (1.00 – 5.50)**
***Ratio (90% CI)**	**110.37 (107.13 - 113.70)**	**114.53 (110.68 - 118.52)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study GRC-BS-021-25 - FED
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Apixaban, 5 mg, tablets, with Eliquis, 5 mg, film-coated tablet, under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 48.00 hours post-dose. Plasma concentrations of apixaban were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2025-05-26 and 2025-06-20.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for apixaban, n=59.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1981.17 ± 379.85**	**207.26 ± 51.12**	**2.50 (0.75 – 12.00)**
Reference	**1913.48 ± 375.63**	**195.75 ± 42.43**	**2.50 (1.00 – 5.00)**
***Ratio (90% CI)**	**103.27 (100.49 - 106.13)**	**105.22 (101.50 - 109.07)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 2.5 mg.

Discussion and overall conclusion
The bioequivalence studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, Apixaban, 5 mg, tablets, could be considered bioequivalent with Eliquis, 5 mg, film-coated tablet.

Absence of studies with the additional strength of 2.5 mg can be acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of apixaban is linear between 2.5 mg and 10 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: Glenmark Arzneimittel GmbH

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

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 Glenmark.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 28 November 2025 and proposed the following summary safety concerns:

Table 1: Summary of Safety Concerns

Important identified risk(s)	• Bleeding
Important potential risk(s)	• Liver Injury • Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	• Use in patients with severe renal impairment

Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate and completely in line with that of the reference product.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning bleeding management and liver injury, which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and additional risk minimisation activities in accordance with the reference product are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 RMP dated 28 November 2025 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Apixaban Glenmark, is found adequate. There are no objections to approval of Apixaban Glenmark, 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.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

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

Post approval commitments
N/A

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

- **Additional risk minimisation measures (including educational material)**
  Details of proposed additional risk minimisation activities
  The Marketing Authorization holder shall ensure that all physicians who are expected to prescribe apixaban are provided with following educational material:
  - Summary of product characteristics
  - Patient Card

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

Key elements of Patient Card
- Signs or symptoms of bleeding and when to seek attention from 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 Glenmark if they need to have any surgery or invasive procedures

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

N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet 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.

The results show that the package leaflet 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.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-