LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Apixaban Devatis
(apixaban)

SE/H/2431/01-02/DC

This module reflects the scientific discussion for the approval of Apixaban Devatis. The procedure was finalised on 2025-02-26. 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, a marketing authorisation has been granted for Apixaban Devatis, 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.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Apixaban Devatis, film-coated tablet, 2.5 mg and 5 mg respectively, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE and NL 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, film-coated tablet, authorised in EU since 2011, with Bristol-Myers Squibb/Pfizer EEIG as marketing authorisation holder.

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

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of apixaban are well known. As apixaban 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)
Since Apixaban Devatis is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study in the fasted state comparing Apixaban Devatis, 5 mg, film-coated tablet, with the reference product Eliquis, 5 mg, film-coated tablet.

Pharmacokinetic properties of the active substance
Absorption: Apixaban has an oral bioavailability of 50 %. 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 0026-22 – 5 MG, FASTING
Methods
This was a single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Apixaban Devatis, 5 mg, film-coated 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 an 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 2022-12-02 and 2022-12-22.

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=30.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1550.2 ± 316.2526**	**157.9 ± 32.2102**	**3.00 (1.33 - 5.00)**
Reference	**1566.7 ± 344.3998**	**164.9 ± 37.0880**	**3.17 (1.00 - 5.00)**
***Ratio (90% CI)**	**99.1 (95.7- 102.6)**	**96.0 (89.7 - 102.7)**	**-**
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 study and its 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 the Apixaban film-coated tablet 2.5 mg and 5 mg product-specific bioequivalence guidance (EMA/CHMP/291499/2018). The bioanalytical methods were adequately validated.

From a pharmacokinetic point of view, it is sufficient to establish bioequivalence with only one strength as the pharmacokinetics of apixaban is linear between 2.5 mg and 10 mg. For drugs with linear pharmacokinetics the bioequivalence study should in general be conducted at the highest strength. The highest strength has been studied which is in accordance with guideline recommendations.

Based on the submitted bioequivalence study, Apixaban Devatis, 5 mg, film-coated tablet, can be considered bioequivalent with Eliquis, 5 mg, film-coated tablet.

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.

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 Devatis.

Part II Safety specification
The MAH has submitted the version 0.3 RMP dated 2024-12-06 and proposed the following summary safety concerns:

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	• 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. It is in line with the RMP of the originator Eliquis.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning bleeding 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 for all safety concerns except for

- Bleeding, where a prescriber guide for HCP and a patient alert card is suggested as aRMM
- Potential risk of bleeding or thrombosis due to overdose or underdose, where a prescriber guide for HCP is suggested as aRMM.

This is in line with the originator and is endorsed.
For details about the conditioned aRMM, please refer to section VI below.

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

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.3 signed 2024-12-06 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Eliquis 2.5 mg film-coated tablets, EMEA/H/C/002148 regarding content and Lenalidomide Devatis 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules, NL/H/4989/001-007/DC regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  The educational material should contain a prescriber guide for HCP and a Patient Alert Card for the patient as follows:

  The Marketing Authorization Holder shall ensure that all physicians who are expected to prescribe apixaban are provided with the following educational material:
  • Summary of Product Characteristics
  • Prescriber Guide
  • Patient Alert Cards

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

  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 Apixaban Devatis 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 and/or caregivers of paediatric 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 Apixaban Devatis 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 Apixaban Devatis if they need to have any surgery or invasive procedure

VII. APPROVAL

The decentralised procedure for Apixaban Devatis, 2,5 mg, 5 mg, Film-coated tablet was positively finalised on 2025-02-26.

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VIII. 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
SE/H/2431/001-002/IB/004	The RMP of Apixaban Devatis is updated following the same change of the RMP of the Reference product ELIQUIS (Bristol-Myers Squibb/Pfizer EEIG, Ireland, MA Numbers: EU/1/11/691/001-015).	No	2026-06-25	Approval	**Variation type IB no C.9.b Obligation/condition, no new data:** The MAH has submitted a Risk Management Plan updated according to the RMP for the reference product Eliquis (EMEA/H/C/002148), version 23.1 (document date: 20 Nov 2025). The submitted RMP, version 1.4 dated 18 May 2026, is considered acceptable. The following condition to the Marketing Authorisation has been updated as a result of this variation application: **Additional risk minimisation measures (including educational material)** 'Prescriber Guide' and 'Summary of product characteristics' have, in line with the reference product, been removed as additional risk minimisation measures (educational material) for the safety concerns *Bleeding* and *Potential risk of bleeding or thrombosis due to overdose or underdose*. The remaining risk minimisation measure (for the safety concern *Bleeding*) has been renamed from 'Patient Alert Card' to 'Patient Card'.