LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Voziberin
(apixaban)

SE/H/2490/001-002/DC

This module reflects the scientific discussion for the approval of Voziberin. The procedure was finalised on 2025-01-22. 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 Voziberin, 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.

The marketing authorisation is granted under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC.

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 Voziberin, 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 concerned member states (CMS) as listed below:

SE/H/2490/001-002/DC – Voziberin (DUPLICATE), CMS: BG, CZ, EE, HR, HU, LT, LV, PL, RO, SI, SK

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 the Union since 2011, 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 Voziberin 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 Voziberin 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 Voziberin, 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 % 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 62322

Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Voziberin, 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 log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 16th May 2023 and 26th May 2023.

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=28

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1492.92 ± 307.10**	**156.52 ± 28.56**	**2.50 (1.00 - 4.50)**
Reference	**1501.87 ± 301.69**	**156.62 ± 29.65**	**3.01 (1.00 - 4.50)**
***Ratio (90% CI)**	**99.36 (95.71-103.15)**	**100.10 (95.86-104.53)**	**-**

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 Voziberin film-coated tablet 2.5 mg and 5 mg product-specific bioequivalence guidance (EMA/CHMP/291499/2018). The bioanalytical methods were adequately validated.

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

The results of study 62322 with 5 mg formulation can be extrapolated to other strength 2.5 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6 and the product-specific bioequivalence guidance for Voziberin film-coated tablet 2.5 and 5 mg (EMA/CHMP/291499/2018).

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 Voziberin.

Part II Safety specification
The MAH has submitted the version 1.0 dated 2025-01-16 for Voziberin 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 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
The MAH has updated the RMP in accordance with the most recent version of the reference product.

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

Conclusion RMP assessment
The submitted Risk Management Plan, version 1.0 dated 2025-01-16 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 and 5 mg film-coated tablets EMEA/H/C/002148 and Rosuvastatin Vivanta 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets NL/H/4158/001-004/DC.

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, Voziberin, is found adequate. There are no objections to approval of Voziberin, 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)**
  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
  - Prescriber Guide
  - Patient alert card

  All patients and/or caregivers of paediatric patients who receive Voziberin 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 doses 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 Voziberin 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 Voziberin if they need to have any surgery or invasive procedure

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

VII. APPROVAL

The decentralised procedure for Voziberin, 2,5 mg, 5 mg, Film-coated tablet was positively finalised on 2025-01-22.

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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/xxxx/WS/1208	RMP has been prepared to update the additional risk minimization measures (aRMMs) to align with the reference product.	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). The submitted RMP, version 2.1 dated 19 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'.