LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Arxebo
(edoxaban tosilate monohydrate)

SE/H/2780/001-003/DC

This module reflects the scientific discussion for the approval of Arxebo. The procedure was finalised at 2026-06-18. 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

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Arxebo, 15 mg, 30 mg, 60 mg, Film-coated tablet.

The active substance is edoxaban, edoxaban tosilate monohydrate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Arxebo is a highly selective, direct and reversible inhibitor of FXa, the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free FXa, and prothrombinase activity. Inhibition of FXa in the coagulation cascade reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation.

Arxebo is authorised for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (see the SmPC for the full indication). It contains the active substance edoxaban and is given by oral administration.

II.2 General comments on the submitted dossier

The application for Arxebo , 15 mg, 30 mg, 60 mg, film-coated tablet, are 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 as concerned member states (CMS):
SE/H/2780: EL

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lixiana, 15 mg, film-coated tablet, authorised in EU since 2015, with Daiichi Sankyo Europe GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Lixiana, 60 mg, film-coated tablet, from EU with Daiichi Sankyo Europe GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 the site responsible for the manufacture and assembly of this product. The RMS has accepted copies of current manufacturer authorisation issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at this site.

GMP active substance
Acceptable QP-declarations are provided.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. GCP-compliance can be considered appropriate based on the inspection history provided.

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 edoxaban are well known. As edoxaban 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 Risk Assessment

Estimation of risk in Phase I is done via the calculation of the Predicted Environmental Concentration in surface water (PECsw) according to the below equation:

$$PECsw = \frac{DOSE_{AS} \cdot F_{PEN}}{WASTEW_{INHAB} \cdot DILUTION}$$

Using the following values:

$DOSE_{AS}$	the maximum daily dose of the active substance consumed per patient (mg patient^{-1} d^{-1})
F_{PEN}	fraction of the population receiving the active substance (default 0.01 patients inh^{-1})
$WASTEW_{INHAB}$	Amount of wastewater per inhabitant per day (default 200 L inh^{-1} d^{-1})
$DILUTION$	dilution factor (default 10)

The maximum daily dose of Edoxaban corresponds to 60 mg of edoxaban daily.

This yields a $PECsw = \frac{60 \cdot 0.01}{200 \cdot 10} = 0.3\ \mu g\ L^{-1}$ which is higher than the action limit (0.01 µg L^{-1}) for further investigation.

Phase II Risk Assessment

Phase II environmental risk assessment has been performed by the MAH of Lixiana® and has been submitted in the EMA in 2014 through the centralized procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004 [4].

The ecotoxicity studies in aquatic environment were conducted following the respective OECD protocols (OECD 209, OECD 210, OECD 211 and OECD 218).

The EMA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev.1) identifies the need to characterize the possible toxicity risks to the surface water compartment, using the Risk Quotient (RQ) equation:

$$RQsw = \frac{PECsw}{PNECsw}$$

The active substance is considered to pose no risk to surface water when the RQ is lower than 1. Since the EC10 value could not be accurately determined, the lowest NOEC value was used to define the PEC and PNEC values for calculation of corresponding RQ-values. RQSW is < 1, and the use of edoxaban does not result in a potential long-term risk to the environment. The innovator's risk assessment data concluded that the Phase II Risk Assessment could not be finalized due to the omission of OECD studies No. 106 and 201. The missing studies have been conducted in 2015 and 2016 respectively, while they have been subsequently submitted to the EMA as well, despite not being published in an updated EPAR. The additional elements submitted included a terrestrial assessment adsorption-desorption study using a Batch Equilibrium Method (OECD 106) including 2 types of sediment sludge and 3 soil types and an ecotoxicity growth inhibition study on algae (OECD 201).

The updated terrestrial assessment concluded that Edoxaban showcases low to medium mobility in soil. The determined KFOC values indicated that no further terrestrial assessment is required, according to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) Table 4 (page 23).

It is the applicant's opinion that the above outcome remains applicable today and for the submitted generic product as well (see Conclusion below).

PBT/vPvB screening

Persistence (Biodegradation)

The logKow for Lixiana® was < 3.0, obtained experimentally using the shake flask method and is accepted. Therefore, definitive PBT/vPvB assessment is not required for edoxaban as the substance is not PBT/vPvB.

Conclusion

No new warnings in the label are proposed for this submission.

Assessor's comment:

Applicant has submitted un updated environmental risk assessment (ERA) report referring to the innovator product (Lixiana®). **For Phase 1,** the MAH of the reference product has used the default FPEN value in the previous assessment, suggesting that the results and the overall ERA outcome remain relevant and applicable for the current generic submission. **The PECsw is >0.01** and a Phase II risk assessment is required. **This is correct.**

A request to access to the previous ERA studies and reports conducted by the MAH of the innovator product has been made, but no data sharing has been agreed. Instead, the Applicant requested the relevant documents from EMA regarding two missing studies for Lixiana® reference product (OECD 106 and OECD 201), however, while the documents cannot be provided without consent from the originator, the relevant information was submitted. The additional elements submitted included a terrestrial assessment adsorption-desorption study using a Batch Equilibrium Method (OECD 106) including 2 types of sediment sludge and 3 soil types and an ecotoxicity growth inhibition study on algae (OECD 201). These studies were conducted in 2015 and 2016 respectively and subsequently submitted to EMA but were not published in EPAR. The updated terrestrial assessment concluded that Edoxaban showcases low to medium mobility in soil. The determined KFOC values indicated that no further terrestrial assessment is required, according to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*). In addition, the partition coefficient value in octanol/water for edoxaban is < 3 (-0.91 at pH 4 and 1.72 at pH 8). Hence, a secondary poisoning assessment is not triggered.

Thus, as pointed out by the Applicant **for Phase II,** the Lixiana reference ERA contains a full Phase II tier A assessment, including the studies that became mandatory in the updated ERA guideline that came into effect in 2024, i.e. including OECD 218 (sediment-dweller toxicity studies), as well as the previously missing studies OECD 106 and OECD 201. The Phase II risk assessment resulted in **RQ values <1, i.e. no risk was identified.**

A complete ERA on edoxaban is available at EMA, this is agreed, and the full reports have been reviewed by assessor. **No new studies are required.**

Conclusions on studies:

The reference product Lixiana ERA is in line with the technical requirements of the 2024 ERA-GL. No new studies are required.

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

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Arxebo with the reference product Lixiana.

Pharmacokinetic properties of the active substance
Absorption: Edoxaban is absorbed with peak plasma concentrations within 1 - 2 hours following oral administration of edoxaban tablets. The absolute bioavailability is approximately 62%.

Food increases peak exposure of edoxaban tablets to a varying extent, but has minimal effect on total exposure. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: Edoxaban displays approximately dose-proportional pharmacokinetics for doses of 15 mg to 60 mg in healthy subjects.

Elimination: The t½ for oral administration is 10 - 14 hours.

Study 64924
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Arxebo, 60 mg, film-coated tablet with Lixiana, 60 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 edoxaban 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 24/09/2024 and 27/10/2024.

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 edoxaban, n=60.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2069.885 ± 550.507**	**257.953 ± 127.222**	**1.33 (0.50- 12.00)**
Reference	**2113.802 ± 470.211**	**280.627 ± 109.351**	**1.00 (0.50 - 12.00)**
***Ratio (90% CI)**	**96.59 (93.02 - 100.30)**	**88.54 (81.36 - 96.37)**	**-**
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 strengths of 15 mg and 30 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). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 15 mg and 30 mg is acceptable, as all conditions for biowaiver for additional strengths, 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 edoxaban is linear between 15 mg and 60 mg.

Based on the submitted bioequivalence study, Arxebo is considered bioequivalent with Lixiana.

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
SE/H/2780, proposed MAH (RMS and EL): Win Medica Pharmaceutical S.A.;

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 Nabaxo and duplicates.

Part II Safety specification
The MAH has submitted the version 0.3 RMP dated 2026-06-05 and proposed the following summary safety concerns:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Bleeding or Bleeding due to: ▪ Drug interaction in combination with other drugs known to increase the risk of bleeding e.g. aspirin, NSAIDs ▪ Inappropriate administration of 60 mg dose/inadvertent overdose by use of 60 mg dose, e.g., in combination with use of strong P-gp inhibitors; in patients with low body weight ≤60 kg; and in patients with moderate to severe renal impairment (CrCL 15–50 mL/min)
Important potential risks	• Hepatic dysfunction • Trend towards decreasing efficacy in NVAF subjects with high CrCL
Missing information	• Lack of reversal agent • Reproductive and development toxicity (Pregnancy and lactation) • Patients with hepatic impairment • Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis) • Patients with mechanical heart valves • Combination with dual antiplatelet therapy • Off-label use in Europe in populations or indications outside the approved indications per European SmPC

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein.

Assessor's comment: Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate.

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

Part V Risk minimisation measures
The applicant has included additional risk minimisation activities in accordance with 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 0.3 signed 2026-06-05 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, Arxebo, is found adequate. There are no objections to approval of Arxebo, 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

- **Additional risk minimisation measures (including educational material)**

Prior to launch of Arxebo in each Member State, the MAH must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the national competent authority (NCA).

The educational programme is aimed at mitigating the risk of serious bleeds or haemorrhage in patients treated with Arxebo by ensuring prescriber awareness and providing guidance on appropriate patient selection, correct dosing as well as management of the risk.
The programme is also aimed at ensuring that the healthcare professionals who intend to prescribe Arxebo are aware of the patient alert card and that the card is to be given to and reviewed with all patients treated with Arxebo.

The MAH shall ensure that in each Member State where Arxebo is marketed, all healthcare professionals who are expected to use Arxebo are provided with the following educational material:

- The Summary of Product Characteristics (SmPC)
- Prescriber guide for healthcare professionals
- Patient alert card

The prescriber guide for healthcare professionals shall contain the following key elements:

- Relevant information on the risk of bleeding
- Details of the population potentially at higher risk of bleeding
- Contraindications
- Recommendations for dose adjustment in at risk populations, including patients with renal or hepatic impairment, low body weight and concomitant use of some P-gp inhibitors
- Guidance on switching from or to Nabaxo treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- Use of coagulation tests and their interpretation
- That all patients should be provided with a patient alert card and be counselled about:
  - The signs or symptoms of bleeding and when to seek attention from a healthcare 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 Arxebo if they need to have any surgery or invasive procedure

The patient alert card should contain the following key safety messages:

- The signs or symptoms of bleeding and when to seek attention
- 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 Arxebo if they need to have any surgery or invasive procedure

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to 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
-	-	-	-	-	-