LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Erjulizam
(edoxaban tosilate monohydrate, edoxaban)

SE/H/2591/001-003/DC

This module reflects the scientific discussion for the approval of Erjulizam. The procedure was finalised on 2025-05-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Erjulizam, 15 mg, 30 mg, 60 mg, Film-coated tablet.

The active substance is edoxaban tosilate monohydrate, edoxaban. 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 Erjulizam, 15 mg, 30 mg, 60 mg, film-coated tablet is a Generic Art. 10(1) applications submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with the following concerned member states (CMS):

Procedure	CMS
SE/H/2591/001-003/DC	CZ, ES, RO

SE/H/2591/001-003/DC included SK as CMS up until Day 198, at which point the applicant withdrew the application there citing business reasons.

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 the Union since 2015, with Daiichi Sankyo Europe GmbH as marketing authorisation holder.

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 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)
Since Erjulizam 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 Erjulizam from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Erjulizam 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 BE/23/115
Methods
This was a single-dose, two-way, fully replicate, crossover study conducted in 48 healthy volunteers, comparing Edoxaban, 60 mg, film coated tablets with Lixiana, 60 mg, film coated tablets 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 ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2023-12-03 and 2023-12-27.

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.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2050.05 ± 545.30**	**329.98 ± 121.22**	**1.25 (0.50-4.00)**
Test (replicated)	**2024.74 ± 592.72**	**307.97 ± 132.19**	**1.13 (0.50-16.00)**
Reference	**2048.79 ± 507.94**	**298.45 ± 103.57**	**1.00 (0.50-3.00)**
Reference (replicated)	**1938.34 ± 524.85**	**282.53 ± 106.22**	**1.01 (0.34-6.00)**
***Ratio (90% CI)**	**101.19 (96.41-106.20)**	**106.44 (96.47-117.44)**	**-**

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 Erjulizam 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.

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 Erjulizam.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 15 November 2024 and proposed the following summary 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, NSAID • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 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 = non-valvular atrial fibrillation; P-gp = P-glycoprotein; SmPC = Summary of Product Characteristics

Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate. The Summary of safety concerns is in line with that of the originator, Lixiana, and is endorsed.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and in accordance with the originator follow-up questionnaires concerning bleeding and hepatic dysfunction, is proposed, 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. Furthermore, educational package for physicians and patients will be implemented as additional risk minimisation measures in the form of Prescriber guide for physicians and patient alert card for patients for the below risks:

1. 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 the 60-mg dose /inadvertent overdose by use of the 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).

2. Missing Information (including reversibility, pregnancy and lactation, hepatic impairment, renal impairment, mechanical heart valves, combination with antiplatelet and off-label use).

See section VII.3 for Key elements.

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

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 15 November 2024 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

For SE/H/2591/01-03/DC one bridging report have been submitted.
Regarding the content the bridging is made to Lixiana 15 mg, 30 mg, 60 mg film-coated tablets (EU/1/15/993/001-030).
Regarding layout the bridging is made to Sitagliptin 25/50/100 mg film-coated tablets (DE/H/6648/001-003/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, Erjulizam, is found adequate. There are no objections to approval of the applications 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)

Prior to launch of Erjulizam 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 Erjulizam 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 Erjulizam are aware of the patient alert card and that the card is to be given to and reviewed with all patients treated with Erjulizam.

The MAH shall ensure that in each Member State where Erjulizam is marketed, all healthcare professionals who are expected to use Erjulizam 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 Erjulizam 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 Erjulizam 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 Edoxaban if they need to
- have any surgery or invasive procedure

VII. APPROVAL

The decentralised procedure for Erjulizam, 15 mg, 30 mg, 60 mg, Film-coated tablet was positively finalised on 2025-05-07.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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