LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sinsferk,
(edoxaban tosilate monohydrate)

SE/H/2613/01-03/DC

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

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

I.1 About the product

Pharmacotherapeutic group: antithrombotic agents, direct factor Xa inhibitors.
ATC Code: B01AF03

Mode of action:
Edoxaban 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.

Claimed indications are:

Sinsferk is indicated in prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

Sinsferk is indicated in treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

I.2 General comments on the submitted dossier

The application for Sinsferk, 15, 30, 60, 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 follows:
SE/H/2613/01-03/DC: DE

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.

The reference product used in the bioequivalence study is Lixiana, 60 mg, film-coated tablet from the German market 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.

I.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.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. The Applicant provided inspection reports from inspections performed by UK MHRA 2019 and US FDA 2022. No issues regarding GCP have been identified.

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 Sinsferk 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 Sinsferk from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single dose of bioequivalence study comparing Edoxaban with the reference product Lixiana.

Pharmacokinetic properties of the active substance
The absolute bioavailability is approximately 62%. Edoxaban is absorbed with peak plasma concentrations within 1 - 2 hours.

Food increases peak exposure to a varying extent but has minimal effect on total exposure. Edoxaban can be taken with or without food. Edoxaban is poorly soluble at pH of 6.0 or higher. Co-administration of proton-pump inhibitors had no relevant impact on edoxaban exposure.

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

The t½ for oral administration is 10 - 14 hours.

Study BE-2299-23
Methods
This was a single-dose, four periods, two-way crossover study conducted in 58 healthy volunteers, comparing Edoxaban, 60 mg, 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 25th October 2023 and 12th November 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 edoxaban, n=106 (Pooled Test), n=108 (Pooled Reference).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3044.0 ± 550.8**	**449.7 ± 128.8**	**1.25 (0.5-6.0)**
Reference	**2972.2 ± 604.2**	**419.7 ± 129.0**	**1.5 (0.5-8.0)**
***Ratio (90% CI)**	**102.96 (100.07-105.94)**	**108.34 (101.89-115.21)**	**-**

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 (BE-2299-23) 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.

Based on the submitted bioequivalence study (BE-2299-23), bioequivalence has been shown.

Absence of study 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 and 60 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

SE/H/2613/01-03/DC:
Proposed MAH: Day Zero ehf.
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 Sinsferk.

Part II Safety specification

Table 3: 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 eg, aspirin, nonsteroidal anti-inflammatory drug (NSAID) • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 60-mg dose, eg 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

Part III Pharmacovigilance Plan

Routine pharmacovigilance, please see below, is suggested. However, in the updated RMP version 1.2 dated 25th November 2024, additional pharmacovigilance activities are proposed by the applicant, which is in line with the reference product and endorsed, please see proposal below:

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Table 4: List of Questionnaires

Safety concern for which the questionnaire is used	Purpose
Bleeding	To follow-up and collect in more details information to further characterise safety concerns.
Hepatic dysfunction	To follow-up and collect in more details information to further characterise safety concerns.

Part V Risk minimisation measures

Table 9: Summary of Additional Risk Minimisation Activities by Safety Concern

Important identified risk: Bleeding or Bleeding Due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding, eg, aspirin, NSAIDs • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 60-mg dose, eg 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)	
Risk minimisation measures	Routine risk minimisation measures SmPC/PIL Prescription only medicine. Additional risk minimisation measures Prescriber Guide Patient Alert Card
Missing information (including reversibility, pregnancy and lactation, hepatic impairment, renal impairment, mechanical heart valves, combination with antiplatelets and off-label use)	
Risk minimisation measures	Routine risk minimisation measures SmPC/PIL Prescription only medicine. Additional risk minimisation measures Prescriber Guide

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted updated Risk Management Plan, version 1.2 signed 25th 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.

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.

V. USER CONSULTATION

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. Assessment of the User Testing was attached in Appendix I in the Day 70 AR.
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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Sinsferk is 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 the following with key elements as specified below:

  Prescriber Guide
  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 Lixiana 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 Lixiana 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 Lixiana if they need to have any surgery or invasive procedure

- **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

VII. APPROVAL

The decentralised procedure for Sinsferk, 15 mg, 30 mg, 60 mg, Film-coated tablet was positively finalised on 2025-01-22.

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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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