LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Edoxaban Sandoz
(edoxaban tosilate monohydrate)

SE/H/2475/01-03/DC

This module reflects the scientific discussion for the approval of Edoxaban Sandoz. The procedure was finalised on 2024-11-27. 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 Edoxaban Sandoz, 15 mg, 30 mg, 60 mg, film-coated tablet.

The active substance is edoxaban tosilate monohydrate. 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 Edoxaban Sandoz 15 mg, 30 mg, 60 mg, film-coated tablet, 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, BE, BG, CZ, DE, DK, EE, ES, FI, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SI and SK as concerned member states (CMS).

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

The reference product used in the bioequivalence studies is LIXIANA 60 mg film-coated tablets from Germany with Daiichi Sankyo Europe GmbH 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 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 Edoxaban Sandoz 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 Edoxaban Sandoz from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Edoxaban Sandoz (Edoxaban Tosylate) with the reference product Lixiana.

Pharmacokinetic properties of the active substance
Absorption: 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.

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 22-VIN-0346 (first study)
Methods
This was a single-dose, two-treatment, two-sequence, two-period, two-way crossover study conducted in 50 healthy volunteers, comparing Edoxaban Tosylate, 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 a 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 10 Dec 2022 and 21 Dec 2022.

Results
For C_{max} the 90% confidence interval for the ratio of the test and reference products fell outside the conventional acceptance range of 80.00-125.00%.

Study 23-VIN-0043 (second study)
Methods
This was a single-dose, two-treatment, two-sequence, four-period full replicate crossover study conducted in 60 healthy volunteers, comparing Edoxaban Tosylate, 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 a 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 30 Mar 2023 and 30 Apr 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=116 (Test), n=117 (Reference).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1822.134 ± 485.7394**	**227.604 ± 100.8668**	**1.250 (0.50 - 12.00)**
Reference	**1758.775 ± 459.4127**	**207.534 ± 86.9737**	**1.250 (0.50 - 16.00)**
***Ratio (90% CI)**	**102.96 (98.38-107.75)**	**109.11 (99.65-119.46)**	**-**

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 studies and the 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 method was adequately validated.

Two bioequivalence studies were performed with the same test and reference products. In the first study (22-VIN-0346), bioequivalence was not demonstrated for C_{max} since the 90% confidence interval for the ratio of the test and reference products fell outside the conventional acceptance range of 80.00-125.00%.

The applicant argues that the first study failed mainly due to underpowered design and the inability to widen the C_{max} acceptance limits. A slightly higher variability and a higher T/R ratio were observed than the assumptions in the sample size calculation. A replicate cross-over design was chosen for the second study. No other factors were identified or discussed. The same test and reference batches were used in both studies. The same analytical method was used for both studies.

It can be agreed that bioequivalence has been demonstrated based on study 23-VIN-0043 with replicated cross-over design which also demonstrated that within-subject variability for C_{max} of the reference product was >30% (thus potentially allowing widening of acceptance criteria for C_{max}, although this was not necessary as results of this study were within conventional acceptance criteria).

Based on the submitted bioequivalence study 23-VIN-0043, Edoxaban Sandoz is considered bioequivalent with Lixiana.

Absence of studies with the additional strengths of 15 mg and 30 mg is acceptable, as all conditions for biowaiver for additional strength(s), 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.

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 Edoxaban Sandoz.

Part II Safety specification
The MAH has submitted the version 1.1 signed RMP dated 22 January 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, 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 toward decreasing efficacy in nonvalvular atrial fibrillation (NVAF) subjects with high CrCl.
Missing information	Lack of reversal agent.
	Reproductive and development toxicity (Pregnancy and breastfeeding).
	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.

With consideration taken to the data in the safety specification the safety concerns listed by the MAH are appropriate and in line with 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 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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 1.1 signed 22 January 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.

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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 Lixiana, EMEA/H/C/002629 and Oxycodone Sandoz house style PL, DE/H/1154.

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, Edoxaban Sandoz, is found adequate. There are no objections to approval of Edoxaban Sandoz 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 Edoxaban Sandoz 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 Edoxaban Sandoz 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 Edoxaban Sandoz are aware of the patient alert card and that the card is to be given to and reviewed with all patients treated with Edoxaban Sandoz.

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

VII. APPROVAL

The decentralised procedure for Edoxaban Sandoz, 15 mg, 30 mg, 60 mg, film-coated tablet was positively finalised on 2024-11-27.

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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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