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Public Assessment Report

Scientific discussion

Edoxaban Kern Pharma 15 mg film-coated tablets
Edoxaban Kern Pharma 30 mg film-coated tablets
Edoxaban Kern Pharma 60 mg film-coated tablets

(Edoxaban tosylate)

ES/H/0989/001-003/DC

Date: 04/12/2025

This module reflects the scientific discussion for the approval of Edoxaban Kern Pharma 15 mg, 30 mg and 60 mg film-coated tablets. The procedure was finalised at 10 September 2025. For information on changes after this date, please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Edoxaban Kern Pharma 15 mg, 30 mg and 60 mg film-coated tablets, in the treatment of the following indications:

- *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).*
- *in treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults*

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as film-coated tablets containing 20.205 mg, 40.41 mg or 80.82 mg of Edoxaban tosylate, corresponding to 15 mg, 30 mg and 60 mg of Edoxaban.
The maximum daily dose is 60 mg/day.
The film-coated tablets are packaged in blisters blister of 250 µm PVC film heat-sealed to an aluminum foil of 20 µm.

II.2 Drug Substance EDOXABAN TOSYLATE

The ASMF procedure is used to support the quality of the drug substance.

General Information

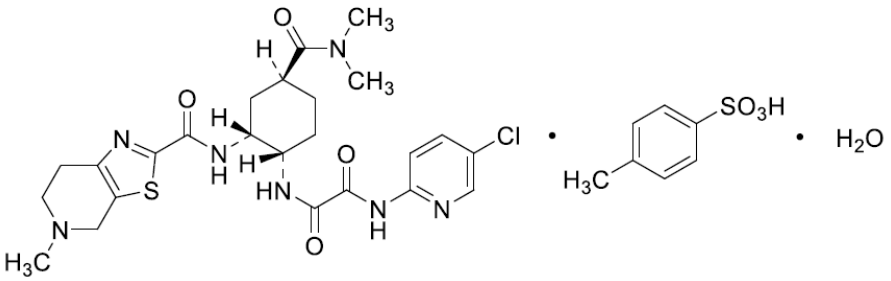
Nomenclature:

INN: Edoxaban Tosilate

Chemical name: N-(5-Chloropyridin-2-yl)- N-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamido)cyclohexyl)oxalamide 4-methylbenzenesulfonate monohydrate

CAS-No: 1229194-11-9

Structure:



Molecular formula: C24H30ClN7O4S·C7H8O3S·H2O

Molecular weight: 738.27

General Properties:
White to light yellow crystalline powder.
Slightly soluble in water and methanol, very slightly soluble in acetonitrile and anhydrous ethanol.
Slightly hygroscopic.

Manufacture, process controls and characterization
The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profiles of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis
Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system
The active substance is packaged in double-lined low-density polyethylene (LDPE) bags (inner layer is transparent and outer layer is black) separately sealed with plastic strip in a fiber drum. The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability
Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

II.3 Medicinal Product

Description of the product
Edoxaban film-coated tablets are immediate release tablets intended for oral administration. The pharmaceutical form is film-coated tablet containing 20.205 mg, 40.41 mg or 80.82 mg of Edoxaban tosylate, corresponding to 15 mg, 30 mg and 60 mg of Edoxaban. The excipients used in the core and in the film-coating are excipients normally used in solid oral dosage forms and are the following: mannitol, starch pregelatinised, crospovidone, hydroypropylcellulose, magnesium stearate and Opadry. Composition of the different coating excipients Opadry is defined. The tablet of 30 mg can be divided into equal doses.
Composition of the different doses is presented, including the function of the excipients in the formulations.

Pharmaceutical Development
The development of the product has been properly described.
Drug substance was evaluated for key physicochemical properties, which can influence in the performance of the drug product and aid in the selection of the product development strategy.
Discussion on key parameters, especially solubility, particle size distribution and polymorphism is presented.
As Edoxaban tosylate tosylate is a BCS class IV substance (low solubility, low permeability), particle size is a drug substance attribute that could affect CQAs of the drug product. Therefore, particle size distribution has been included in the drug substance specification.

Edoxaban tosylate is known to exist in 2 different polymorphic forms (form I and form II). Edoxaban tosylate used by the applicant corresponds to polymorphic form I. The crystalline form has been checked in the active substance as well as in the finished product. The results of the polymorphism study by XRD have been presented. Drug product show that the crystalline form is maintained during the manufacture of the finished product and that it is the same as the reference medicinal product.

Manufacture of the product
The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Excipients
Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis
The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system
The primary packaging consists of a blister of 250 µm PVC film heat-sealed to an aluminum foil of 20 µm.
The bulk container consists of a double PE bag inside a HDPE drum (as the secondary packaging).
Exemplar certificates of analysis for the different parts of the container closure system, their IR spectra and certificates of suitability for food contact and European compliance are provided.

Stability
Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 30 months.

Storage conditions: This product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of edoxaban are well known. As edoxaban is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Edoxaban Kern Pharma 15 mg, 30 mg and 60 mg film-coated tablets is a generic product, it will not lead to an increased exposure to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Edoxaban is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.
The Applicant has submitted a comparative, randomized, four-period, two-treatment, two-sequence, single-dose, open-label, fully-replicated bioequivalence study of Edoxaban 60 mg film-coated tablets versus Lixiana 60 mg film-coated tablets in healthy subjects under fasting conditions.

IV.2 Pharmacokinetics

Biowaiver
This application concerns three strengths: 15 mg, 30 mg and 60 mg strengths, and the bioequivalence study has been carried out with the 60 mg strength.

The criteria according to the *Guideline on the Investigation of Bioequivalence* for waiving the 15 mg and 30 mg strengths are fulfilled as:

- The strengths are manufactured with the same process.
- The qualitative composition of all the strengths is the same.
- The composition of the strengths is quantitatively proportional.
- Appropriate dissolution profiles between the different strengths have confirmed to be similar.

Bioequivalence studies

Study EDOX23015

GCP compliance
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities
The clinical and analytical parts of the study were performed at Arab Pharmaceutical Industry Consulting/ Pharmaceutical Research Unit, 19 Yajooz Street, Al-jubaiha, P.O Box 1084 Sweileh 11910 Jordan.

Design
A randomized, two treatment, four period, two-sequence, single dose, fully replicated crossover bioequivalence study was carried out under fasting conditions in 50 healthy male and female subjects, aged 18– 44 years. The medication was administered as a single dose by oral route with 240 mL of water for reference or test film-coated tablets in sitting posture after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of at least 7 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
50 subjects were included in the study. 50 subjects were treated; samples of the 49 subjects who completed at least one period with test and one period with reference were analyzed and included in the pharmacokinetic and statistical analysis.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Descriptive statistics

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	Reference Product
$AUC_{(0\text{-}72h)}$ (ng·h/mL)	1467.836 (±370.296)	1394.671 (±350.688)
C_{max} (ng/mL)	270.743 (±98.063)	255.475 (±94.782)
T_{max} [a] (hours)	1.33 (0.50-8.00)	1.33 (0.50-6.00)

[a]Median (Min, Max)

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals (%)
$AUC_{(0\text{-}72)}$	105.94	101.40-110.69
C_{max}	108.13	99.36-117.69

Based on the submitted bioequivalence study, Edoxaban Kern Pharma 60 mg film-coated tablets, when compared with the Reference Product in fasting conditions seems to meet the bioequivalence criteria with respect to the Cmax and AUC.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study, Edoxaban Kern Pharma film-coated tablets is considered bioequivalent with the Reference Product.

IV.3 Pharmacodynamics/ Clinical efficacy/ Clinical safety

No new clinical data have been provided and none is required for this type of generic application.
The submitted clinical documentation based on scientific literature is sufficient and acceptable regarding clinical information.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 0.2, 14 May 2025), 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 Kern Pharma 15 mg, 30 mg and 60 mg film-coated tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding eg, aspirin, 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

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding eg,	SmPC sections 4.3, 4.4, 4.5, 4.8 and 4.9 PL: sections 2, 3 and 4 Prescription medicine only	Prescriber Guide Patient Alert Card

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
aspirin, 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	SmPC Sections 4.2, 4.4 and 4.8 PL: sections 2 and 4 Prescription medicine only	Prescriber Guide
Trend towards decreasing efficacy in NVAF subjects with high CrCL	SmPC Section 4.4 Prescription medicine only	None
Missing Information		
Lack of reversal agent	SmPC Section 4.4 Prescription medicine only	Prescriber Guide
Reproductive and development toxicity (Pregnancy and lactation)	SmPC Sections 4.3, 4.6 and 5.3 PL: section 2 Prescription medicine only	Prescriber Guide
Patient with hepatic impairment	SmPC Sections 4.2, 4.4 and 5.2 PL: section 2 Prescription medicine only	Prescriber Guide
Patients with severe renal impairment (CrCL <30 mL/min) or endstage renal disease (CrCL <15 mL/min or on dialysis)	SmPC Sections 4.2 and 5.2 PL: section 2 Prescription medicine only	Prescriber Guide
Patients with mechanical heart valves	SmPC Section 4.4 PL: section 2 Prescription medicine only	None
Combination with dual antiplatelet therapy	SmPC Section 4.5	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Prescription medicine only	
Off-label use in Europe in populations or indications outside the approved indications per European SmPC	Risk not addressed in labelling Prescription medicine only	None

- Only routine pharmacovigilance activities are proposed.

IV.5 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Lixiana 15 mg, 30 mg 60 mg film-coated tablets (Parent PIL-1) and Linezolid Kern Pharma 600 mg film-coated tablets (Parent PIL-2). Lixiana 15 mg, 30 mg 60 mg film-coated tablets (Parent PIL-1) was used for key safety messages, and Linezolid Kern Pharma 600 mg film-coated tablets (Parent PIL-2) was used for design and layout. The bridging report submitted by the applicant has been found acceptable.
Based on the above justification the daughter PIL is considered comparable with the parent PILs and assessed as readable in compliance with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product edoxaban is found adequate. There are no objections to the approval of Edoxaban Kern Pharma film-coated tablets 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.

The results of the study with the 60 mg strength can be extrapolated to the 15 mg and 30 mg strengths, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.