IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Edoxaban Tiefenbacher 30 mg film-coated tablets
Edoxaban tosylate monohydrate
PA1178/020/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Edoxaban Tiefenbacher 15mg, 30mg & 60mg Film-coated Tablets from Alfred E. Tiefenbacher (GmbH & Co. KG) on 2nd May 2025 for:

The 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), and in the 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).

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a 'generic' application.

The application is through the Decentralised Procedure with Ireland acting as reference member state (RMS) and DE, EE, HR, HU, IS, LT, LV, RO, SI, SK as concerned member states (CMS).

The reference product used in the bioequivalence study is LIXIANA 60 mg film-coated tablets (Daiichi Sankyo Europe GmbH as marketing authorisation holder) authorised in the Union since 2015.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Edoxaban Tiefenbacher 15mg, 30mg & 60mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Edoxaban tosilate monohydrate
Pharmacotherapeutic classification (ATC code)	B01AF03
Pharmaceutical form and strength(s)	15mg, 30mg & 60mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1178/020/001-003
Marketing Authorisation Holder	Alfred E. Tiefenbacher (GmbH & Co. KG)
MRP/DCP No.	IE/H/1331/001-003/DC
Reference Member State	IE
Concerned Member State	DE, EE, HR, HU, IS, LT, LV, RO, SI, SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Edoxaban Tiefenbacher 15mg, 30mg & 60mg Film-coated Tablets.

II.2 Drug substance

The active substance is edoxaban tosilate monohydrate, an established active substance manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current regulatory requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each tablet contains either 15 mg, 30 mg or 60 mg of edoxaban as edoxaban tosolate monohydrate.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Edoxaban 15 mg, 30 mg and 60 mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Edoxaban 15mg, 30mg & 60mg film-coated tablets on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of edoxaban tosylate monohydrate are well known.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Edoxaban Tiefenbacher 15mg, 30mg & 60mg film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of edoxaban tosilate monohydrate are well known. As edoxaban tosilate monohydrate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Edoxaban tosilate monohydrate is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lixiana 15 mg, 30 mg, 60 mg film-coated tablets authorised in the Union since 2015, with Daiichi Sankyo Europe GmbH as marketing authorisation holder.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Edoxaban Tiefenbacher is compared with the pharmacokinetic profile of the reference product Lixiana.

An open label, randomized, four-period, two-treatment single dose oral bioequivalence study of Edoxaban 60 mg film-coated tablets and Lixiana 60 mg Filmtabletten under fasting conditions was carried out. Based on the pharmacokinetic parameters of the active substance the reference tablet Lixiana and the test tablet Edoxaban Tiefenbacher are bioequivalent with respect to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 15 mg and 30 mg strengths are dose proportional with the 60 mg strength. The pharmacokinetics of the active substance are linear in the product strength range and the results of the bioequivalence study performed with the 60 mg strength therefore apply to the other strengths.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lixiana.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Edoxaban is absorbed with peak plasma concentrations within 1 - 2 hours following oral administarion of edoxaban tablets. The absolute bioavailability is approximately 62%.
There is no clinically relevant accumulation of edoxaban with once daily dosing. Steady state concentrations are achieved within 3 days.

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

After taking renal function and body weight into account, age had no additional clinically significant effect on edoxaban pharmacokinetics.

Patients with mild or moderate hepatic impairment exhibited comparable pharmacokinetics and pharmacodynamics to their matched healthy control group. Edoxaban has not been studied in patients with severe hepatic impairment.

After accounting for body weight, gender had no additional clinically significant effect on edoxaban pharmacokinetics.

IV.3 Pharmacodynamics

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. Edoxaban produces rapid onset of pharmacodynamic effects within 1 - 2 hours, which corresponds with peak edoxaban exposure (C_{max}).

IV.4 Clinical Efficacy

A a generic application, no new applicant-generated efficacy studies were submitted in this application.

IV.5 Clinical Safety

The overall safety profile of edoxaban is established. No additional safety clinical studies to demonstrate safety have been included in the application and none were required.

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 15mg, 30mg, 60 mg film coated tablets.

Safety specification

Summary of safety concerns	
Important identified risks	Bleeding or Bleeding due to: • Drug interaction in combination with other drug known to increase the risk of bleeding eg. Aspirin, NSAID • Inappropriate administration of the 60mg dose/inadvertent overdose by use of the 60mg 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 dysfuction • 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

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection include targeted follow-up questionnaires for the important identified risk of bleeding and potential risk of hepatic dysfunction.

Additional risk minimisation measures (aRMM) to mitigate the risk of serious bleeds or haemorrhage are deemed necessary and consist of:
- Educational programme for healthcare professionals and patients (Prescriber's guide and Patient alert card).

Periodic safety update reports (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.

IV.6 Discussion on the clinical aspects

This decentralised marketing authorisation application has been submitted in accordance with Article 10.1 of Directive 2001/83/EC. A bioequivalence study has shown pharmcokinetic equivalence of the test 60 mg product with the reference product LIXIANA 60 mg film-coated tablets (Daiichi Sankyo Europe GmbH) authorised in the Union since 2015. The biowaiver requirements to enable assumption of the same pharmacokinetic behaviour of the 15 mg and 30 mg tablets with the 60 mg tablet have been met.

V. OVERALL CONCLUSIONS

Edoxaban Tiefenbacher Film-coated Tablets are generic forms of LIXIANA Film-coated Tablets (Daiichi Sankyo Europe GmbH) which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considers Edoxaban Tiefenbacher 15 mg, 30 mg and 60 mg Film-coated Tablets the same as the reference products and has therefore granted a marketing authorisation.

VI. REVISION DATE

20.03.2030