HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

Cagluen 15 mg, 30 mg, 60 mg
film-coated tablets

(edoxaban tosilate)

HU/H/0985/001-003/DC

Date: 15.09.2026

This module reflects the scientific discussion for the approval of Cagluen 15 mg, 30 mg, 60 mg film-coated tablets. The procedure was finalised at 07.10.2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cagluen 15 mg, 30 mg, 60 mg film-coated tablets from Viatris Limited.

Indications:
The product 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).

The product 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).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lixiana 15 mg, 30 mg, 60 mg film-coated tablets, registered by Daiichi Sankyo Europe GmbH since 2015-06-19 (EU/1/15/993/001-030). The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia and Romania.
The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

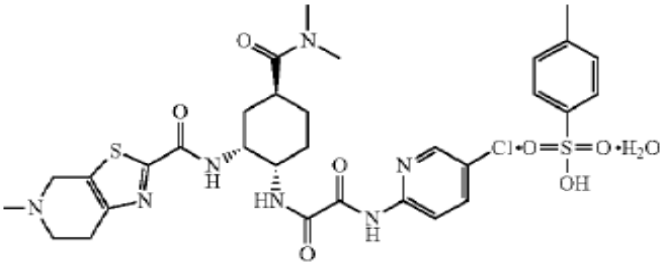
The chemical-pharmaceutical assessment report concerns the application of Edoxaban 15 mg, 30 mg and 60 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application).
Reference products are Lixiana film-coated tablets (containing 15 mg, 30 mg and 60 mg of edoxaban as active ingredient, in the form of tosilate monohydrate) which were the original products of Daiichi Sankyo Europe GmbH.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Edoxaban tosilate monohydrate
Chemical name: N'-(5-chloropyridin-2-yl)-N-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-[(5-methyl-6,7-dihydro-4H-[1,3]thiazolo[5,4-c]pyridine-2-carbonyl)amino]cyclohexyl]oxamide;4-methylbenzenesulfonic acid; hydrate

Structure:



The active substance is white to yellowish crystalline powder, soluble in dimethylsulphoxide, soluble in methanol, very slightly soluble in methylene dichloride and ethanol and insoluble in water. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy, mass spectroscopy (MS), infrared spectroscopy (IR), elemental analysis (CHN), and X-ray powder diffraction (XRPD). The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Edoxaban tosilate monohydrate is not official in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, identification, water content, sulphated ash, related substances, enantiomeric purity, p-toluene sulphonic acid content, assay, residual solvents, particle size distribution, polymorphic form identification, and microbiological purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of edoxaban tosilate monohydrate is acceptable if stored in its original package, protected from light.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop film-coated tablets containing edoxaban as drug substance in 15 mg, 30 mg or 60 mg doses, in the form of tosilate monohydrate, bioequivalent and pharmaceutically equivalent to the reference medicinal product Lixiana film-coated tablets, the branded original products of Daiichi Sankyo Europe GmbH.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

- 15 mg: Orange, round-shaped film-coated tablets debossed with “15” on one side and plain on the other side, with a diameter of 6.6 mm ± 5 %.

• 30 mg: Pink, round-shaped film-coated tablets debossed with “30” on one side and plain on the other side, with a diameter of 8.4 mm ± 5 %.
• 60 mg: Yellow, round-shaped film-coated tablets debossed with “60” on one side and plain on the other side, with a diameter of 10.4 mm ± 5 %.

The excipients used in the finished product are mannitol, hydroxypropilcellulose, crospovidone, pregelatinised maize starch, colloidal anhydrous silica, and magnesium stearate. Coating materials consist of carmellose sodium, maltodextrin, glucose monohydrate, soya lecithin, calcium carbonate, and iron oxides. All excipients used comply with their respective European Pharmacopoeia monograph or with the requirements of EC/231/2012. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure systems of the product are Aluminium-PVC/PE/PVDC blisters or High Density Polyethylene (HDPE) bottles with child-resistant PP closures. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with no special storage conditions is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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)

The applicant has provided a statement and has not conducted an in depth environmental risk assessment in accordance with regulatory guidelines (EMEA/CHMP/SWP/4447/00 Rev. 1). Since Edoxaban PharOS 15 mg, 30 mg, 60 mg film-coated tablets are intended for generic substitution, this

will not lead to an increased exposure to the environment. An in depth environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

This product is a generic formulation of Lixiana which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional nonclinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Edoxaban is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.
For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Pivotal bioequivalence study was conducted in order to compare the bioavailability of Edoxaban 60 mg film-coated tablets and Lixiana® 60 mg film-coated tablets in healthy male volunteers under fasting conditions.
The study is an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral comparative bioequivalence study of Edoxaban 60 mg film-coated tablets (PharOS Ltd., Greece) and Lixiana® 60 mg film-coated tablets (Marketing Authorization Holder: Daiichi Sankyo Europe GmbH, Germany) in healthy male volunteers under fasting conditions.

A biowaiver is requested for the 15 mg and the 30 mg formulation of Edoxaban based on the above bioequivalence study.

<u>Biowaiver</u>

One pivotal bioequivalence study has been submitted for the 60 mg strength.
The applicant claims that bioequivalence of the other strengths, 15 mg and 30 mg, can be concluded since all conditions for biowaiver of additional strength according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled.

<u>Bioequivalence study</u>

The study is an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral comparative bioequivalence study of Edoxaban 60 mg film-coated tablets (PharOS Ltd., Greece) and Lixiana® 60 mg film-coated tablets (Marketing Authorization Holder: Daiichi Sankyo Europe GmbH, Germany) in healthy male volunteers under fasting conditions.
The study was conducted with 120 (114 completed) male subjects in accordance with protocol. After an overnight fasting of at least 10 hours, a single 60 mg oral dose of investigational product was administered to the subjects in a sitting posture with about 240 mL of water at ambient temperature under the supervision of trained study personnel in each study period.

Blood samples were collected at pre-dose (0.0 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 30.0 and 36.0 hours after administration of each dose. The interval between doses were 06 days in Group-1 (Period-1 to 2) and 05 days in Group-2 (Period-1 to 2). The plasma samples were shipped to the Bioanalytical facility for analysis.

Plasma concentrations of edoxaban were determined with a LC-MS/MS method using edoxaban D6 as internal standard. K_2EDTA was used as anticoagulant. Calibration standard range was 5.000 ng/mL to 600.0 ng/mL

Pharmacokinetic Variables

- Primary pharmacokinetic parameters: Cmax, and AUCt
- Secondary pharmacokinetic parameters: AUCi, Tmax, Kel, AUC_%Extrap_obs and tHalf

The statistical analysis was performed using SAS® statistical software (Version: 9.4; SAS Institute Inc., USA). The SAS PROC GLM procedure was used for the analysis of variance. The study power calculations and the 90% confidence interval calculations were based on the least-squares means values generated by the SAS LSMEANS option to the SAS PROC GLM procedure and the standard error of the estimate as given by the PROC GLM procedure.
Ln-transformed data of Cmax and AUCt were evaluated statistically using the PROC GLM from SAS® for difference due to treatment, period, sequence and subject(sequence) as fixed effects.
Treatment and period were tested using Mean Square Error and sequence was tested using subject(sequence) as the error term at 5% level of significance.
Bioequivalence criteria: The 90% confidence interval of the relative mean (geometric least square mean) of the test to reference formulation for Ln-transformed pharmacokinetic parameters Cmax and AUCt was to be within 80.00% to 125.00% for Edoxaban to establish bioequivalence.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1617.072(±386.296)	1670.311 (±380.154)	287.257 (±93.535)	1.250 (0.500-8.00)
Reference	1603.642 (±377.201)	1656.542 (±373.712)	273.407 (±83.579)	1.500 (0.500-5.00)
***Ratio (90% CI)**	100.76 (97.34 -104,30)		104.76 (98.56-111.36)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

Overall, Edoxaban 60 mg Film-Coated Tablets were well tolerated as a single oral dosage(1×60 mg) administered under fasting condition in both test and reference formulation.

Conclusion
Based on the results, the test formulation Edoxaban 60 mg film-coated tablets is considered to be bioequivalent to the reference formulation LIXIANA (Edoxaban) 60 mg Film-coated tablets.
Absence of studies with the additional strengths is acceptable from a pharmacokinetic point of view.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.4 Clinical efficacy

No new efficacy study has been performed by the applicant.

IV.5 Clinical safety

No new safety data have been submitted by the applicant.

IV.6 Pharmacovigilance

Product's name: Cagluen 15 mg, 30 mg and 60 mg film-coated tablets
Active substance: edoxaban
MAH: Viatris Limited
Reference number: HU/H/0985/001-003/DC

1. Summary of Pharmacovigilance System

Viatris Limited has submitted a signed Summary of the Applicant's/MAH Pharmacovigilance System (dated 19.04.2022, version number: 5.0). Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

2. Risk Management Plan (version number: 0.3, date of sign-off: 13.08.2024)

- **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, 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 NV AF 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 endstage 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

The list of safety concerns is line with the safety concerns of reference product on the EU RMP for Lixiana and Roteas (Daiichi Sankyo Europe GmbH, Berlin-Chemie AG) version 17.0 (Data lock point: 31/12/2022, Date of final sign off: 21/07/2023) last updated on the EMA website on 10.01.2024.

➢ Pharmacovigilance Plan

Routine pharmacovigilance activities (with two adverse event follow-up questionnaires: "Bleeding" and "Hepatic dysfunction") is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

➢ Risk Minimisation Measures

Additional risk minimisation measures (including educational material)

Prior to launch of Cagluen 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 Cagluen 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 Cagluen are aware of the patient alert card and that the card is to be given to and reviewed with all patients treated with Cagluen.
The MAH shall ensure that in each Member State where Cagluen is marketed, all healthcare professionals who are expected to use Cagluen 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 Cagluen 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 Cagluen 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 Cagluen if they need to have any surgery or invasive procedure

Details of local dissemination and exact content of the educational materials should be agreed with the national competent authorities in the national phase of this decentralised procedure.

3. PSUR

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lixiana. No new clinical studies were conducted. The MAH demonstrated through bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lixiana is a well known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0985/001-003/WS/001 (HU/H/xxxx/WS/053)	B.II.b).2.a). .Replacement or addition of a site where batch control/testing takes place	2025.05.09	2025.06.08	Approved
HU/H/0985/001-003/IA/003	B.II.b).2.a). . Replacement or addition of a site where batch control/testing takes place	2025.12.01	2025.12.31	Positive
HU/H/0985/001-003/WS/002 (HU/H/xxxx/WS/092)	C.I.z).Other variation	2025.01.12	2025.02.11	Approved
HU/H/0985/001-003/WS/004 (HU/H/xxxx/WS/111)	B.I.b).1.b).Tightening of specification limits, B.I.d).1.z).Other variation	2026.06.04	2026.07.03	Approved