COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Gledohib 15 mg, 30 mg and 60 mg, film-coated tablets (edoxaban tosilate monohydrate)

## NL/H/6115/001-003/DC

## Date: 31 March 2026

**This module reflects the scientific discussion for the approval of Gledohib 15 mg, 30 mg and 60 mg, film-coated tablets. The procedure was finalised on 10 September 2025. For information on changes after this date, please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ASMF | Active Substance Master File |
| BE | Bioequivalence |
| CBG /MEB | College ter Beoordeling van Geneesmiddelen /The Medicines Evaluation Board |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State(s) |
| CrCL | Creatinine clearance |
| DCP | Decentralised Procedure |
| eAF | Electronic Application Form |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| ERA | Environmental Risk Assessment |
| ERP | European Reference Product |
| FUQ | Follow-Up Questionnaire |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) |
| LALA | Locally applied, locally acting products |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board |
| NSAID | Non-steroidal anti-inflammatory drug |
| NVAF | Non-valvular atrial fibrillation |
| PAR | Public Assessment Report |
| P-gp | P-glycoprotein |
| Ph.Eur. | European Pharmacopoeia |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PL | Package Leaflet |
| PSURs | Periodic safety update reports |
| QC | Quality control |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| RMS | Reference Member State |
| SPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |
| USP/NF | United States Pharmacopoeia/National Formulary |

*Note: Not all abbreviations may apply for this PAR.*

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gledohib 15 mg, 30 mg and 60 mg, film-coated tablets, from G.L. Pharma GmbH.

The products are indicated for:

- 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).
- 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 up-to-date indications and posology is given in the SPC.

# II. EXECUTIVE SUMMARY

## II.1 Rationale for the product

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP) Lixiana 60 mg film-coated tablets, which has been registered via the centralised procedure EU/1/15/993 by Daiichi Sankyo Europe GmbH since 19 June 2015.

To support the application, the MAH has submitted the results of a bioequivalence study (BE) with the 60 mg strength product and reference Lixiana 60 mg and a justification for biowaiving of the additional lower strengths 15 mg and 30 mg.

This application has been assessed with The Netherlands as Reference Member State (RMS) and Austria as Concerned Member State (CMS).

Scientific advice (Annex 5.14) was given by European Medicines Agency (EMA) for this product according to the electronic Application Form (eAF) (not Quality related).

## II.2 About the product

Edoxaban is a selective, direct and reversible inhibitor of Factor Xa (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.

Pharmaco-therapeutic group (ATC Code): B01AF03 – Edoxaban.

# III. QUALITY ASPECTS

## III.1 Introduction

Gledohib are film-coated tablets. Each tablet contains edoxaban tosilate monohydrate equivalent to 15 mg, 30 mg or 60 mg edoxaban tosilate as drug substance. The tablets of the different strengths can be distinguished by their colour, size and debossing and are as follows:

Gledohib 15 mg:
orange colour, round biconvex coated tablets (approximately 6 mm), debossed with “7X” on one side and “L” on the other side.

Gledohib 30 mg:
pink colour, round biconvex coated tablets (approximately 8 mm), debossed with “7X” on one side and “I” on the other side.

Gledohib 60 mg:
yellow colour, round biconvex coated tablets (approximately 10 mm), debossed with “7X” on one side and “H” on the other side.

The excipients are:

*Tablet core* - mannitol, hydroxypropylcellulose, crospovidone, silica colloidal anhydrous and magnesium stearate.

*Coating ingredients* - macrogol poly(vinyl alcohol) grafted copolymer (E1209), titanium dioxide (E171), kaolin heavy, copovidone sodium laurilsulfate, iron oxide yellow (E172) (only for the 15 mg and 60 mg strengths) and iron oxide red (E172) (only for the 15 mg and 30 mg strengths).

The cores of the different tablet strengths are qualitatively the same and quantitatively proportional.

The film-coated tablets are packed in polyvinyl chloride/ aluminium (PVC/Al) blisters or perforated unit dose blisters, consisting of a transparent, colourless PVC top foil with an aluminium (Al) lidding foil, the blister are packed in cartons.

## III.2 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described. The dug substance is edoxaban tosilate monohydrate, an established substance not described in the European Pharmacopoeia. The drug substance is a white or pale yellowish crystalline powder and is very slightly soluble in water. Edoxaban

tosilate monohydrate exhibits polymorphism. For this product, polymorphic form I is consistently produced. Edoxaban tosilate monohydrate exhibits three chiral centra, it has been adequately justified that racemisation of a chiral centre during drug product manufacturing or storage is considered negligible and hence control of stereochemistry in the drug product is not needed.

Manufacturing process

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents. No class 1 organic solvents or heavy metal catalysts are used in the process.

Quality control of the drug substance

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods are sufficiently described and are considered suitably. Non-compendial methods has been adequately validated. The active substance specification is considered adequate to control the quality and meets the in-house requirements set by the MAH. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches. This is acceptable.

Stability of the drug substance

Stability data on the active substance have been provided for three pilot scale batches and one full scale batch in accordance with the applicable European guidelines. Based on the data submitted, the re-test period for the drug substances was confirmed for 24 months when stored under the stated conditions. This is acceptable.

## III.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients is justified, and their functions are explained. The main development studies were for the optimisation of the manufacturing process and development of the dissolution method used to support the bioequivalence study. The development studies and manufacturing process are described in sufficient detail.

Manufacturing process

The manufacturing process has been sufficiently described and critical steps are identified. The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. The main steps are sieving, blending and compression followed by film-coating and packaging.
Process validation data on the product have been presented for three batches of the lower limit of the batch size range for each tablet strength and in accordance with the relevant European guidelines. Process validation for the upper limit of the batch size range will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements. Iron oxide yellow and red meet the requirements of Regulation (EU) No 231/2012. These specifications are acceptable.

Quality control of the drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, assay, related substances, dissolution and uniformity of dosage units. The release and shelf-life tests and limits are identical with the exception of the tests for related substances. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product.

An adequate risk evaluation report on nitrosamines has been submitted. Appropriate tests for nitrosamine presence are performed on the final product. Furthermore, an adequate risk evaluation report on elemental impurities has been submitted. Since the total elemental impurity level from all sources in the drug product is calculated to be consistently less than 30% of the Permitted Daily Exposure (PDE), additional controls are not required.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data for three batches of the lower limit of the batch size range of each tablet strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of the drug product

Stability data on the product have been provided for three production scaled batches of each tablet strength stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Furthermore, photostability studies were performed in accordance with ICH recommendations. The results showed that the product is stable when exposed to light. Based on the data submitted, a shelf life was granted of 2 years. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability

According to the SPC section 5.2, the tablets may be crushed and mixed with water or apple puree and immediately administered orally to patients who are unable to swallow whole tablets. Alternatively, the tablets may be crushed and suspended in at least 10 mL of water for one tablet, and administered through a nasogastric tube or gastric feeding tube made of different materials (polyvinylchloride, silicone and polyurethane) within a range of 8-12 French diameter, after which it should be rinsed two times with at least 20 mL of water. For these special handling of the medicinal product, assay and recovery data have been provided demonstrating that the suspension of crushed tablet in water or apple puree, stored at room temperature, is stable for up to 4 hours after preparation. This is acceptable.

Compatibility with silicone, polyurethane (PU) and polyvinylchloride (PVC) enteral feeding tubes of crushed tablets suspended in water and apple puree has been demonstrated. Suspension and flush volumes are included in the SPC and package leaflet (PL).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

### III.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gledohib has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

## IV. NON-CLINICAL ASPECTS

### IV.1 Ecotoxicity/environmental risk assessment (ERA)

Since Gledohib is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

### IV.2 Discussion on the non-clinical aspects

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

## V. CLINICAL ASPECTS

### V.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 member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

## V.2 Pharmacokinetics

The MAH conducted one bioequivalence study in which the pharmacokinetic profile of the test product Gledohib 60 mg, film-coated tablets, G.L. Pharma GmbH(Austria) was compared with the pharmacokinetic profile of the reference product Lixiana 60 mg film-coated tablets, Daiichi Sankyo Europe GmbH (Germany). A biowaiver was requested for the lower strengths 15 mg and 30 mg.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and manufacturing process of the bioequivalence batch was identical to the formula proposed for marketing and at a representative production scale.

**Biowaiver**
Edoxaban tosilate monohydrate has been classified as an BCS Class IV compound (low solubility/low permeability).

According to the EMA Bioequivalence guideline, the following general requirements must be met where a waiver for additional strength is claimed:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Based on the results of a bootstrapping procedure comparing the dissolution of four tablets 15 mg edoxaban and two tablets 30 mg edoxaban with one tablet 60 mg edoxaban at pH 6.8, the similarity of the dissolution at pH 6.8 was confirmed as the calculated $f_2$ similarity factor values were within criteria (>50). An $f_2$ value between 50 and 100 suggests that the two dissolution profiles are similar. As the conditions for the biowaiver criteria are met, a biowaiver for the lower strengths 15 mg and 30 mg has been granted.

Bioequivalence study under fasted conditions, study 0339-22
*Design*
A single-dose, open label, randomised, two-treatment, four-period, two-sequence, full replicate, bioequivalence study was carried out under fasted conditions. 32 healthy participants (27 males and 5 females) aged 18-45 years were dosed. Each participant received a single dose (60 mg) of one of the two edoxaban tosilate monohydrate formulations. The tablet was orally administered after overnight fasting for at least 10 hours. The participants were refrained from drinking water from 1 hour before to 1 hour after dose administration in each period except for the 240 ± 2 after mL water provided with drug administration. The tablet was swallowed whole, without chewing or crushing. There were four dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose (0 hr) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SPC edoxaban may be administered without reference to food intake. From the literature it is known that food does not interact with the absorption of edoxaban. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

*Analytical/statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
A total of 32 participants were included in the study. 31 Participants were included in the pharmacokinetic analysis, as they completed at least two treatment periods (one with the reference and one with the test formulation). 29 Participants completed all four treatment periods and 2 participants completed three treatment periods. 1 Participant completed only one period and was therefore not eligible for pharmacokinetic analysis. 3 Participants were discontinued from the studies (2 participants in period III and 1 participant in period IV) due to mild adverse events not related to the study treatment. Samples from the withdrawn participants were also analysed.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of edoxaban (as tosilate monohydrate), 60 mg under fasted conditions.**

| **Treatment N=31** | **$AUC_{0-t}$** (ng.h/mL) | **$AUC_{0-\infty}$** (ng.h/mL) | **$C_{max}$** (ng/mL) | **$t_{max}$** (h) |
|---|---|---|---|---|
| **Test** | 1963±372 | 2001±362 | 250±78.8 | 1 (0.5 - 12) |
| **Reference** | 1996±381 | 2031±376 | 252±88.7 | 1.5 (0.5 - 12) |
| ***Ratio (90% CI)** | 98.3 (93.52 – 103.30) | 98.6 (93.97-103.44) | 99.7 (89.10 – 111.52) | - |

| | |
|---|---|
| **$AUC_{0-\infty}$** | Area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 72 hours |
| **$C_{max}$** | Maximum plasma concentration |
| $t_{max}$ | Time after administration when maximum plasma concentration occurs |
| CI | Confidence interval |

**ln-transformed values*

Conclusion on bioequivalence study:
Pharmacokinetic concentration time profiles for edoxaban have adequately been characterised and the 90% confidence intervals calculated for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of the

test and reference products are within the acceptance range of 80.00-125.00% for $AUC_{0-t}$ and 75.18-133.01% for $C_{max}$.

Based on the submitted bioequivalence study Gledohib 60 mg film-coated tablets is considered bioequivalent with Lixiana 60 mg film-coated tablets. Bioequivalence was shown appropriately.

As a biowaiver has been granted, the results of the study with the 60 mg formulation (study nr. 0339-22) can be extrapolated to the lower strengths 15 mg and 30 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

## V.3 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 Gledohib. At the time of approval, the accepted version of the RMP was with data loss prevention (DLP) 4 November 2024 and sign off date 20 January 2025.

**Table 2. Summary of safety concerns, additional Pharmacovigilance (PhV) and Additional Risk Minimisation Measures aRMM**

| Summary of safety concerns | | FUQ / Additional PhV | aRMM |
|---|---|---|---|
| Important identified risks | Bleeding or bleeding due to:<br>• Drug interaction in combination with other drugs known to increase the risk of bleeding e.g.: aspirin, NSAID.<br>• Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 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). | FUQ | Prescriber Guide and Patient alert Card |
| Important potential risks | • Hepatic dysfunction<br>• Trend towards decreasing efficacy in NVAF subjects with high CrCL. | FUQ<br>None | None |
| Missing information | • Combination with dual antiplatelet therapy<br>• Lack of reversal agent<br>• Off-label use in Europe in populations or indications outside the approved indications per European SmPC<br>• Patients with hepatic impairment<br>• Patients with mechanical heart valves<br>• Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis)<br>• Reproductive and development toxicity (pregnancy and lactation). | None | Prescriber Guide |

*Abbreviations: CrCL: creatinine clearance; FUQ: Follow-Up Questionnaire; NSAID: non-steroidal anti-inflammatory drug; NVAF: non-valvular atrial fibrillation; P-gp: P-glycoprotein; SmPC: Summary of Product Characteristics.*

Pharmacovigilance Plan

List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC.

**Additional risk minimisation measures (including educational material):**

Prior to launch of Edoxaban 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 Gledohib 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 Gledohib are aware of the patient alert card and that the card is to be given to and reviewed with all patients treated with Gledohib.

*Educational material*
The MAH shall ensure that in each Member State where Gledohib is marketed, all healthcare professionals who are expected to use Edoxaban are provided with the following educational material:

- The Summary of Product Characteristics (SmPC)
- Prescriber guide for healthcare professionals
- Patient alert card.

*The prescriber guide*
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 Gledohib 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 if they need to have any surgery or invasive procedure.

*Patient alert card*
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 Gledohib if they need to have any surgery or invasive procedure.

### V.4 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 a 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.

## VI. USER CONSULTATION

The package leaflet (PL) 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report making reference to Lixiana 15 mg, 30 mg and 60 mg film-coated tablets, EU/1/15/993 (EMEA/H/C/002629/0000) for content and to Clozapine 12.5 mg orodispersible tablets (NL/H/4200-4204/001-005/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

## VII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gledohib 15 mg, 30 mg and 60 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Lixiana 60 mg film-coated tablets. 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.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, based on the data submitted, considered that essential similarity has been demonstrated for Gledohib with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 September 2025.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| N.A. | N.A. | N.A. | N.A. | N.A. | N.A. |