LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Empagliflozin Labiana
(empagliflozin)

SE/H/2694/001-002/DC

This module reflects the scientific discussion for the approval of Empagliflozin Labiana. The procedure was finalised at 2025-12-17. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Empagliflozin Labiana, 10 mg, 25 mg, Film-coated tablet.

The active substance is empagliflozin. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Mechanism of action

Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into circulation. In patients with type 2 diabetes and hyperglycemia a higher amount of glucose is filtered and reabsorbed.

Pharmacological classification

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03

II.2 General comments on the submitted dossier

The application for Empagliflozin Labiana, 10 mg, 25 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Jardiance, 25 mg, film-coated tablet, authorised in the Union since 2014, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that

acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

The applicant has provided a non-clinical overview and an ERA document.

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of empagliflozin are well known. As empagliflozin 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.

Shortly, empagliflozin is a selective inhibitor of SGLT2 (sodium-glucose co-transporter 2), which

plays a major role in glucose reabsorption in the kidneys. Inhibition of renal SGLT-2 has the effect of blocking glucose reuptake from the glomerular filtrate leading to increased excretion of glucose in the urine, a concept that has been exploited to reduce hyperglycaemia in patients with type 2 diabetes mellitus. With regard to ADME, of note is that a study (Kuoni et al, 2024) on ex-vivo human placental transfer with SGLT2 inhibitors, empagliflozin crossed the placental barrier within 360 min (relatively slow, but reaching foetal circulation).

With regard to Toxicology, empagliflozin repeat-dose exposure of rodents and dogs (13 to 52-weeks weeks exposure depending on species) indicates that kidneys and liver are toxicological target organs. Chronic renal and vascular findings in rats and mice suggest limited safety margins for these effects: <17x in rats and <4.4x in mice. No indications of genotoxicity have been found. In rats (2-year study), empagliflozin acted as a non-genotoxic carcinogen, increasing the incidence of interstitial cell tumours in a way that was correlated with decreased body weight gain, which is known to induce such tumours in the Wistar rat strain. The carcinogenic process for these tumours in rat is deemed to be of little relevance for human safety. In another rat study (Yadav et al, 2024), empagliflozin exposure generated male testicular Leydig cell cancers – which has also been noted with other SGLT2 inhibitors - that increased numerically by empagliflozin at 26x and 42x MRHD. The formation of the Leydig tumours in humans is very rare, but the toxicological/clinical relevance remains somewhat unclear. In mice (2-year study), empagliflozin generated male mouse-specific renal tumours – also likely in a non-genotoxic manner - that have not been observed with other SGLT2 inhibitors, indicating a unique mechanism of action for empagliflozin. The neoplasms may be linked to chronic tubular injury and regenerative processes (supported by an in-depth 13-week follow-up study in mice).

For DART, male and female fertility, as well as early embryonic development, were unaffected in rats at doses up to 700 mg/kg/day (155x MRHD). Empagliflozin did not demonstrate teratogenic potential in embryofetal development studies conducted in rats and rabbits, even at the highest tested doses (700 mg/kg). Effects on foetuses were limited to a few cases of bent limb bones in rats and post-implantation loss in one rabbit, both occurring at the highest maternally toxic dose levels. In a pre- and postnatal toxicity study in rats, empagliflozin caused minimal and transient reductions in pup body weight gain without long-term effects on development, learning, or memory. Potential exposure via milk was also investigated, and plasma levels of empagliflozin in rat pups on postnatal day 18 were below quantifiable limits, even at maternal doses up to 100 mg/kg/day. Although transient learning and memory deficits were observed in male pups at PND21, no deficits were apparent at PND62, indicating no lasting functional impairment.

The non-clinical sections of the SmPC follow those of the reference product (Jardiance).

Environmental Risk Assessment (ERA)

The procedure, and the ERA, is applicable to the RMS (SE) and CMS (PT). This application was initiated after the activation of the 2024 CHMP ERA GL and the provided ERA should therefore be in line with its guidance. Based on being an Art 10 procedure, the ERA-document identifies that there exists a previous ERA (Jardiance 10 mg and 25 mg film-coated tablet from Boehringer Ingelheim International GmbH, product approved 22 May 2014). It can be noted that the EPAR for Jardiance includes an ERA-result table for up to Phase IIA under the 2006 CHMP ERA GL framework.

The present product (Empagliflozin Labiana 10 mg, 25 mg film coated tablets (Labiana Pharmaceuticals) and the reference product (Jardiance) are therapeutically equivalent, and they share the same administration route, same pharmaceutical form, same indications, in the same patient population, at the same dosages and with identical maximum daily dose. As such, it is considered unlikely that the relevance of the PEC values used in the Jardiance ERA have changed or that overall environmental exposure has increased. With regard to the novel technical requirements in the 2024

CHMP ERA GL (compared to the 2006 CHMP ERA GL), an assessment has been made that no new requirements have been triggered.

Overall, the conclusions of the reference (Jardiance) ERA – no environmental risk in surface water, groundwater, STP effluent, and sediment - are considered applicable to the presently proposed product (justified in an ERA document dated 22/7-2025).

Overall conclusion
There are no objections to approval of Empagliflozin Labiana from a non-clinical point of view.

III.3 Clinical aspects

BCS-based biowaiver
The application is based on a BCS (Biopharmaceutical Classification System)-based biowaiver and no bioequivalence study has been submitted. The applicant claims that empagliflozin is a BCS class III-drug substance.

According to the ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a BCS class III-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and low permeability (BCS class III). Also, *in vitro* dissolution characteristics of the test and the reference product should be very rapid, and excipients should be qualitatively the same and quantitatively similar.

Background/Applicant's justification
To support a BCS class III-based biowaiver, the applicant provides the following information:
The application is eligible for a BCS-based biowaiver as the criteria established in the "Guideline On the Investigation of Bioequivalence" (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, January 2010) and the scientific guideline "ICH M9 on biopharmaceutics classification system based biowaivers" (EMA/CHMP/ICH/493213/2018) are met:

- Empagliflozin is a BCS Class III active substance.
- The proposed medicinal product is formulated as an immediate-release oral dosage form with systemic action.
- The drug product is a dosage form that is pharmaceutically equivalent to the reference product.

Discussion and overall conclusion
The justification for BCS (Biopharmaceutics Classification System)-based biowaiver can be accepted. From a pharmacokinetic perspective, the active substance can be classified as a BCS class III substance, and the active substance does not have a narrow therapeutic index. Since the composition is qualitatively the same and quantitatively very similar a BCS class III-based biowaiver is possible. For quality aspects of the BCS- biowaiver, please see the Quality section.

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.

Pharmacovigilance system
Proposed MAH: Labiana Pharmaceuticals S.L.U.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies

with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan (RMP), 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 Empagliflozin Labiana.

Part II Safety specification
There are no safety concerns for Empagliflozin Labiana.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 21/07/2025, 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.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Empagliflozin Labiana, is found adequate. There are no objections to approval of Empagliflozin Labiana, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 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)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet 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. The language used for the purpose of user testing the PL was Spanish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-