EDA Assessment Report for human medicinal product

(Scientific Discussion)

Empodiab 25mg Film Coated Tablets

(Empagliflozin)

Date: November 2023

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Empodiab 25mg Film Coated Tablets from Penta Pharma Egypt.
- The product contains the active substance "Empagliflozin" which is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is a white to off-white colour powder, which is soluble in methanol, slightly soluble in ethanol, insoluble in toluene, very slightly soluble in water, slightly soluble in acetonitrile & soluble in acetonitrile/water mixture (50%). It non- hygroscopic in nature and it contains six chiral carbons in its structure, hence it shows stereoisomerism.
- The synthesis of drug substance includes six steps to produce through the formation of three isolated intermediate. The two starting materials, all reagents, solvents & catalysts are well controlled.
- The drug substance is elucidated via elemental analysis, UV, Infrared spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H & ^{13}C) and mass spectroscopy, and the structure is well characterized. The polymorphism is confirmed via P-XRD.
- The drug substance specifications include the following tests: description, solubility, identification (by IR and enantiomeric purity), water content (Karl Fischer), sulphated ash, specific optical rotation enantiomeric purity (HPLC), assay (HPLC), related substances (HPLC), acetic acid content (HPLC), residual solvents (by GC) and particle size distribution (PSD) test. all limits are acceptable.
- All analytical procedures were adequately described and well validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- The API is packed in white - coloured low-density polyethylene bag with ties, followed by black- coloured low-density polyethylene bag and this double polyethylene bag is placed in triple laminated aluminum pack with heat sealed, and this triple laminated aluminium pack is placed in a HDPE container and close with lid. Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.

- Stability of API is submitted (accelerated at 40°C±2°C / 75±5%RH and long term at 25°C±2°C / 60±5%RH) and conclude the conformity of specifications during the retest period and storage conditions.

Medicinal Product

Product Description

- Empodiab 25mg Film Coated Tablets are available as a white, round, biconvex, non -scored film coated tablets for oral administration, containing 25mg of Empagliflozin per tablet.
- The product is packed in (transparent PVC/PVD/Aluminium) strips, each strip contains 10 film coated tablets.
- The excipients are: lactose monohydrate "200 mesh", microcrystalline cellulose PH 102, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide 200 & magnesium stearate (for Tablet core) and Opadry white "hydroxypropyl methylcellulose (HPMC), titanium dioxide & triacetin" (for tablet coat).

Pharmaceutical development

- The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

Manufacturing process

- The manufacturing process includes two stages (Mixing, wet granulation, compression & coating).
- The manufacturing process was adequately validated by FPP manufacturer according to relevant guidelines for three primary batches.

Control of excipients

- All excipients used comply with USP pharmacopeia except for Opadry white which is In-house. The specifications of the excipients are well justified.

Product specification

- Product specification includes the four universal tests for description, identification (by HPLC & UV), assay, impurities and additional tests including: mass uniformity, disintegration, loss on drying, dissolution (HPLC), uniformity of dosage units (by content uniformity-HPLC), and microbiological limits. All limits are acceptable.
- Analytical methods were adequately described and well validated.

- Batch Analysis from the proposed production site were provided for three primary batches, demonstrating compliance with the release specifications.
- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.
- Stability of the finished pharmaceutical product is submitted (accelerated at 40°C±2°C / 75±5%RH and long term at 30°C±2°C / 65±5%RH) and conclude the conformity of specifications during the shelf-life and storage conditions.
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, a declaration/certificate of TSE/BSE free is submitted for substances of animal origin.

Conclusion:
Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

Introduction

Empagliflozin is well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
Empagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise also used to reduce the risk of stroke, heart attack, or death in people who have type 2 diabetes along with heart and blood vessel Disease.
Empagliflozin is also approved to reduce the risk of cardiovascular mortality and hospitalization in adults with heart failure with reduced ejection fraction regardless of whether or not the patient has concomitant diabetes. Empagliflozin is not approved for use in patients with type 1 diabetes.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Empodiab 25mg Film Coated Tablets (Empagliflozin 25mg) Manufactured by: Penta Pharma, Egypt. relative to the reference product Jardiance® 25 mg Film coated tablets (Empagliflozin 25mg) Produced by: Boehringer Ingelheim Pharma GmbH Germany, administered to healthy participants.

Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Two-Sequence, Two Period, crossover bioequivalence study with a washout period of one week between periods under fasting conditions in healthy participants.

On randomized manner each subject received single oral dose from test & reference products directly into mouth administrated by 240 ml water after overnight fasting (at least 8-10 hours in fasting) according to the randomization sheet.
Blood Sampling: pre-dose blood sample were withdrawn at 0.00, 15 min, 30 min, 45 min, 1 hr, 1:30, 2, 2:30, 3, 3:30, 4, 5, 6, 7, 9, 11, 24, 48 & 72 hours after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Empagliflozin in subject samples were executed according to international guidelines and official publications.

CRO developed an adequately validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Empagliflozin 25 mg** under fast conditions.

Treatment N=33	AUC0-t (ng.h/ml)	AUC0-inf (ng.h/ml)	Cmax (ng/ml)	tmax (h)	$T_{1/2}$ (h)
Test	1852.20	2287.76	197.40	5	7.36
Reference	1841.96	2253.30	212.33	5	6.53
***Ratio (90%) CI**	99.123 (89.723 - 109.507)	101.777 (92.784 - 111.642)	91.931 (84.270 - 100.289)	--------	---------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for C_{max}, AUC $_{0\text{-}t}$ and AUC $_{0\text{-}inf}$ are within the bioequivalence acceptance range of 80 % - 125 %.
Based on this study demonstrated that Empagliflozin 25mg in product dosage form of The Test Product Empodiab 25mg Film Coated Tablets Manufactured by Penta Pharma, Egypt relative to The Reference Product Jardiance® 25mg Film coated tablets (Empagliflozin 25mg) Produced by: Boehringer Ingelheim Pharma GmbH Germany, administered to healthy participants on 33 participants.