Arab Republic of Egypt
Egyptian Drug Authority
CAPP

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الصيدلية

EDA Assessment Report for Human Medicinal Product

(Scientific Discussion)

Diglifloz Plus XR Extended Release Film Coated Tablets

(Dapagliflozin 10mg (as Propanediol monohydrate) **+**

Metformin Hydrochloride 1000mg)

Date: September 2023

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Diglifloz Plus XR Extended-Release Film Coated Tablets from Marcyrl Pharmaceuticals Industries.

Diglifloz Plus XR is a combination of dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

II. Quality Aspect

Drug Substance

Diglifloz Plus XR contains two drug substances, dapagliflozin propanediol monohydrate and metformin hydrochloride.

1- Dapagliflozin propanediol monohydrate,

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance (Dapagliflozin) is White, off-white to yellow powder, highly soluble in methanol, soluble in ethanol, acetonitrile, slightly soluble in water. It has five stereo genic centers and exhibits polymorphism.
- The synthesis of drug substance (Dapagliflozin) includes single step. All starting materials, reagents, solvents are well controlled.
- The drug substance (Dapagliflozin) is elucidated via Elemental analysis, Mass spectroscopy, FT-IR, UV Spectroscopy, ^{1}H-NMR, ^{13}C-NMR, X -ray powder diffraction, DSC, TGA and the structure is well characterized.
- The drug substance (Dapagliflozin) specifications are in accordance with In-house specifications and include the following tests: Description, Solubility, Identification, Water content, Residue on ignition, Assay by HPLC, Propanediol content, Related substances, Residual solvents, Microbiological tests, XRPD & Particle size distribution tests. All acceptance criteria are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 3 batches demonstrating compliance with the current drug substance specifications.
- 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 and conclude the conformity of specifications during the shelf life and storage conditions

2- Metformin Hydrochloride

The APIMF (Applicant/ restricted part) has been submitted for evaluation.

- The drug substance (Metformin) is white crystalline powder, freely soluble in water, slightly soluble in ethanol, practically insoluble in acetone and in methylene dichloride. It has no chiral centers and exhibit polymorphism.
- The synthesis of drug substance (Metformin) includes single step that has seven sub stages. All starting materials, reagents, solvents are well controlled.
- The drug substance (Metformin) is elucidated via Elemental analysis, Mass spectroscopy, FT-IR, UV Spectroscopy, ^{1}H-NMR, X -ray powder diffraction, DSC and the structure is well characterized.
- The drug substance (Metformin) specifications are in accordance with British Pharmacopeia and include the following tests: Appearance, Solubility, Identification, Appearance of solution, Loss on drying, Sulfated ash, Assay by Potentiometry, Related substances, Nitrosamines impurities, Residual solvents, Microbiological tests & Particle size distribution test. All acceptance criteria are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 3 batches demonstrating compliance with the current drug substance specifications.
- 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 and conclude the conformity of specifications during the shelf-life and storage conditions.

Medicinal Product

- **Product Description**
  - Diglifloz Plus XR Extended release film coated tablets are slightly buff to greyish buff oblong biconvex coated tablet with core consist of white Dapagliflozin layer and slightly buff Metformin layer.
  - The product is packed in a carton box containing 1,2 or 3 AL/AL strips each of 7 or 10 extended-release film coated tablets and insert leaflet.
  - **The excipients for Metformin layer**: Carboxymethyl Cellulose Sodium, HPMC, Colloidal Silicone Dioxide, Quinoline yellow lake, Magnesium Stearate and Purified Water.
  - **The excipients for Dapagliflozin layer**: Lactose Anhydrous, Microcrystalline Cellulose, Crospovidone, Colloidal Silicone Dioxide and Magnesium Stearate.
  - **The excipients for coating layer:** Opadry AMP yellow and Purified water.
- **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 includes:
  - Metformin Layer is done by Milling, dry mixing, wet granulation, drying, milling mixing and final blending.
  - Dapagliflozin Layer is done by sieving, mixing and final blending.
  - Direct compression of the two-layer followed by Coating.

- Control of excipients, all excipients comply with USP except for the coloring and film coating agents, the specifications of the excipients are justified.

- Product specification includes the four universal tests for description, identification, assay, Impurities (Related substances and Nitrosamines impurities) and additional tests: uniformity of mass, uniformity of dosage units, water content, dissolution test and microbiological tests. All acceptance criteria are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site was provided for 3 primary batches demonstrating compliance with the release specification.
- Container closure system is suitable to store FPP and comply with food grade packaging material and the specifications are acceptable.
- Stability of FPP is submitted and conclude the conformity of specifications during the shelf life and storage conditions.
- A certificate of TSE/BSE free is submitted for substances of animal origin.

Recommendation:
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. The 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

Dapagliflozin & Metformin Hydrochloride are well-known active substances with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature.

Dapagliflozin & Metformin Hydrochloride is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Test Product Diglifloz plus XR 10/1000mg Extended-Release Film Coated Tablets (Manufactured by: Marcyrl Pharmaceutical Industries, Egypt) versus Reference Product Xigduo® XR

10/1000mg Extended-Release Tablets (Manufactured by: AstraZeneca Pharmaceuticals, U.S.A.) administered to healthy participants.

Design

A Comparative, Open-Label, Single Dose, Randomized, Two-Treatment, Un-Replicate Four-Period, Crossover Bioequivalence study under fasting and fed conditions with a washout period of one week between periods in healthy participants.

Route of administration: each volunteer will receive one tablet of test product Diglifloz plus XR 10/1000mg Extended-Release Film Coated Tablets and one tablet of reference product Xigduo® XR 10/1000 mg Extended-Release Tablets with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing according to the randomization sheet.

Analytical Methods

All procedures used to perform the bio-analyses of Dapagliflozin 10mg (as Propanediol monohydrate) & Metformin Hydrochloride 1000mg 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. The bioequivalence study accordance with acceptable standards of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Fasted State Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Dapagliflozin** 10mg XR-Film Coated Tablet under **fasting** conditions.

Treatment N=26	AUC_{0-t} ng.h/ml	AUC_{0-inf} ng.h/ml	C_{max} ng/ml	T_{max} (hr)	$t_{1/2}$ (hr)	k_{el} (hr)
Test	439.29333± 99.937	494.63427± 106.004	138.66 ± 24.74	1.00	8.07± 3 .97	0.11249± 0 .062
Reference	439.04984± 106.073	517.28216± 198.421	139.03 ±40.23	1.00	11.20± 17.08	0.11865± 0.078
***Ratio (90%) CI**	100.34 (93.58-107.59)	98.53 (88.08-110.23)	101.91 (92.82-111.9)	---------	---------	---------
CV (%)	22.7	21.4	17.8	---------	---------	---------

*ln-transformed values
* Volunteers withdrawn from the study: Vol.3 withdrawn at Phase II.
No. of volunteers included in PK and statistical calculation: 25 volunteers

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Metformin** 1000mg XR-Film Coated Tablet under **fasting** conditions.

Treatment N=26	**AUC0-t ng.h/ml**	**AUC0-inf ng.h/ml**	**Cmax ng/ml**	**Tmax (hr)**	**t1/2 (hr)**	**k_{el} (hr)**
Test	10178.38629± 3850.294	10978.63655± 4356.821	1289.14 ± 507.61	4.00	8.54 ± 4.27	0.10268± 0.056
***Ratio (90%) CI**	90.3 (84.15-96.9)	91.84 (84.67-99.61)	100.59 (91.91-110.08)	---------	---------	
CV (%)	37.8	39.7	39.4	---------	----------	

*ln-transformed values
Volunteers withdrawn from the study: Vol.3 withdrawn at Phase II.
No. of volunteers included in PK and statistical calculation: 25 volunteers

Fed State Results

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Dapagliflozin** 10mg XR-Film Coated Tablet under **fed** conditions.

Treatment N=26	**AUC0-t ng.h/ml**	**AUC0-inf ng.h/ml**	**Cmax ng/ml**	**Tmax (hr)**	**t1/2 (hr)**	**k_{el} (hr)**
Test	481.71506± 139.884	533.48480± 146.583	82.71± 23.85	2.75	8.51± 4.05	0.10160± 0 .052
Reference	454.15034± 9 6.46 7	522.57754± 121.5 32	85.15± 2 5.51	2.50	12.04± 12.72	0.08550± 0 .039
***Ratio (90%) CI**	104.12 (97.48-111.22)	100.82 (94.33-107.76)	97.29 (87.39-108.31)	---------	---------	
CV (%)	29	27.5	28.8	---------	----------	

*ln-transformed values

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Metformin** 1000mg XR-Film Coated Tablet under **fed** conditions.

Treatment N=26	AUC0-t ng.h/ml	AUC0-inf ng.h/ml	Cmax ng/ml	Tmax (hr)	t1/2 (hr)	k_{el} (hr)
Test	15348.41246± 6206.961	15960.47659± 6345.774	1254.78± 470.73	7	7.93± 3.30	0.10125± 0.039
Reference	14988.68704± 5902.642	15687.31486± 5811.098	1271.04 ±488.96	6.50	9.47± 10.04	0.10080± 0.039
***Ratio (90%) CI**	101.72 (94.18-109.86)	100.45 (93.1-108.38)	99.21 (93.59-105.18)	---------	----------	---------
CV (%)	40.4	39.8	37.5	---------	----------	---------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for C_{max}, AUC_{0-t} and AUC_{0-inf} are within the bioequivalence acceptance range of 0.80 – 1.25.

Based on this study demonstrated that Dapagliflozin 10mg & Metformin Hydrochloride 1000mg in XR-Film Coated Tablet of the test product, Diglifloz Plus XR 10/1000mg Extended Release Film Coated Tablets (Manufactured by: Marcyrl Pharmaceuticals Industries, Egypt) & reference product, Xigduo® XR 10/1000mg Extended Release Tablets (Manufactured by AstraZeneca Pharmaceuticals, USA) are Bioequivalent after a single an oral dose of test and reference administration under Fasting & Fed conditions on healthy participants.