EDA Assessment Report for Human Medicinal Product

(Scientific Discussion)

Covalmet Film Coated tablets

(Vildagliptin 50mg & 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 Covalmet 50/1000mg Film Coated tablets from Copad Egypt for trade & pharmaceutical industries (COPAD Pharma).

The product is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes whose diabetes is not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.

II. Quality Aspect

Drug Substance

1-Metformin HCl:

- APIMF (applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white crystal powder freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride. It exhibits polymorphism.
- The synthesis of drug substance includes two steps with the formation of one intermediate. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Mass spectroscopy, FT-IR, UV Spectroscopy, ^{1}H-NMR, XRPD, ^{13}C-NMR and the structure is well characterized.
- The drug substance specifications are in accordance with Metformin Hydrochloride European Pharmacopeia monograph/In-House and include the following tests: description, solubility, identification with (melting point, IR, TLC, color test & chloride test), specific optical rotation, appearance of solution, loss on drying, sulphated ash, assay by HPLC, related substances and residual solvents. All limits are acceptable.
- Analytical methods were adequately described and validated.
- 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-Vildagliptin:

- APIMF (applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to slightly yellowish crystalline powder non-Hygroscopic, freely soluble in dimethyl sulfoxide and methanol, soluble in water, sparingly soluble in tetrahydrofuran and isopropyl alcohol, insoluble in hexanes and cyclohexane. Vildagliptin exhibits polymorphism.
- The synthesis of drug substance includes one step. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via FT-IR spectroscopy, UV spectroscopy, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy and Elemental analysis and the structure is well characterized.
- The drug substance specifications are in accordance with “In-house” specifications and include the following tests: description, identification with IR & HPLC, loss on drying, residue on ignition, assay by HPLC, related substances, enantiomeric impurity, residual solvents, particle size test and microbiological tests. Benzene is tested as skip test. All limits are acceptable.
- Analytical methods were adequately described and validated.

- 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

- Covalmet is oblong non-scored white to off-white biconvex tablets.
- The product is packed in carton box containing strip (AL/ OPA/Al/PVC) of 10 film coated tablets with insert leaflet.
- The excipients are: microcrystalline cellulose, polyvinylpyrrolidone, sodium stearyl fumarate (in tablet core) and hypromellose, polyethylene glycol 6000, titanium dioxide, yellow iron oxide, ethanol 95% & purified water (in 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 is done by mixing, sieving, wet granulation, sieving, blending and coating.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three primary sized batches.
- Control of excipients, all excipients comply with USP except for polyethylene glycol 6000 & ethanol 95% comply with BP and the specifications of the excipients are justified.
- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests: mass uniformity, disintegration, dissolution, uniformity of dosage units, residual solvents, nitrosamine impurities & microbial tests. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for 3 primary sized batches demonstrating compliance with the release specification.
- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.
- Stability of finished pharmaceutical product is submitted 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, 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.

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

Vildagliptin/Metformin are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Vildagliptin/Metformin are indicated for type II diabetes mellitus.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Covalmet (50/1000mg) Film Coated Tablets (Manufactured by: Copad Egypt for Trade & Pharmaceutical Industries (COPAD Pharma)) relative to Galvus Met (50/1000mg) Film Coated Tablet Marketing Authorization Holder: Novartis Pharma AG, Basel, Switzerland. administered to healthy participants.

Design

Comparative, Open-Label, Single Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, Two Way Crossover Bioequivalence Study with a Washout Period of One week Between periods Between periods under Fed condition in healthy participants

Route of Administration is Oral with 240 mL of a 20% glucose solution in water upon dosing at room temperature.

Blood Sampling: pre-dose blood sample and 0.50, 1.00, 1.25 ,1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00 ,24.00 hours post dose.

Analytical Methods

All procedures used to perform the bio-analyses of Vildagliptin/Metformin 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).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Metformin** 1000mg and strength under fed conditions.

Treatment N=33	**AUC_{0-t} ng.h/ml**	**$AUC_{0-\infty}$ ng.h/ml**	**C_{max} ng/ml**	**t_{max} hr**	**$t_{1/2}$ hr**
Test	12665.186 (8235.213- 17052.464)	12961.950 (8348.853- 17459.161)	1418.197 (898.880- 2108.370)	4.5 (1.250-6)	3.803 (2.834- 4.437)
Reference	12014.890 (8652.548- 16935.008)	12365.850 (9057.318- 17236.454)	1370.748 (929.916- 2604.109)	4.5 (2-6)	3.892 (2.975- 5.492)
***Ratio (90%) CI**	105.44 (102.04-108.94)	104.60 (101.25-108.07)	104.14 (99.14-109.39)	-------	----------
CV (%)	---------	-------	11.817 %	------	----------

*ln-transformed values

*Thirty-four (34) volunteers were enrolled & participated in the study, Thirty -three (33) who completed all study periods and cross over included in pharmacokinetics and statistical analysis, as Vol. (31) withdrawn before Phase II.

Table 2. Pharmacokinetic parameters of (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Vildagliptin** 50mg under fed conditions.

Treatment N=33	**AUC_{0-t} ng.h/ml**	**$AUC_{0-\infty}$ ng.h/ml**	**C_{max} ng/ml**	**t_{max} hr**	**$t_{1/2}$ hr**
Test	972.460 (702.991 -1554.433)	994.029 (722.148 -1636.819)	212.648 (125.684- 346.092)	2.250 (1.250 -5.500)	2.262 (1.530 -2.993)
Reference	944.946 (682.590- 1345.31)	965.685 (693.357-1431.144)	203.645 (116.951 -370.417	2.500 (1.5- 5)	2.305 (1.519- 3.065)
***Ratio (90%) CI**	102.85 (100.54-105.21)	102.86 (105.19- 100.59)	104.54 (98.14-111.37)	-------	----------
CV (%)	----------	---------	15.229 %	-------	--------

*ln-transformed values

*Thirty-four volunteers (34) were enrolled & participated in the study, Thirty -three (33) who completed all study periods and cross over included in pharmacokinetics and statistical analysis, as Vol. (31) withdrawn before Phase II.

Conclusion

The 90% confidence intervals calculated for C_{max}, AUC $_{0-t}$ and AUC $_{0-inf}$ are within the bioequivalence acceptance range of 80 % - 125 %.

Based on this study demonstrated that the active pharmaceutical ingredient of Vildagliptin/Metformin in film coated tablet of the test product Covalmet (50/1000mg) film coated tablets (Manufactured by: Copad Egypt for Trade & Pharmaceutical Industries (COPAD Pharma)) & reference product Galvus Met (50/1000mg) film coated tablets Marketing Authorization Holder: Novartis Pharma AG, Basel, Switzerland are bioequivalent after a single oral dose of test and reference administration under Fed conditions on 33 participants.