EDA Assessment Report for human medicinal product

(Scientific Discussion)

Virecta Plus 100 mg/60 mg Scored Film Coated Tablets

Sildenafil (as Citrate) & Dapoxetine (as HCl)

Date: August, 2026

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Virecta Plus 100 mg/60 mg Scored Film Coated Tablets from EVAPHARMA for Pharmaceutical Industries (EVAPHARMA).

-The product is only indicated when prescribed by specialized physician for the treatment of premature ejaculation (PE) with erectile dysfunction in adult men aged 18 to 64 years.

II. Quality Aspect

Drug Substance (Sildenafil Citrate)

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is White or almost White, Slightly hygroscopic, crystalline Powder. The API is Slightly soluble in water and in methanol, practically insoluble in hexane. Sildenafil citrate has no chiral center. Sildenafil Citrate exhibits polymorphism, the crystalline form resulting from the manufacturing process adopted by the supplier is form I.
- The synthesis of drug substance includes three stages with the formation of two intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via mass spectrometry (MS), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR), elemental analysis and UV spectroscopy. Moreover, the crystalline form of sildenafil citrate has been confirmed by X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC).
- The drug substance specifications include appearance, solubility, identification (IR), water content (KF), sulphated ash, impurity E (TLC), related substances (HPLC), assay (HPLC), residual solvents (GC), X-ray diffraction, microbiological tests and particle size distribution.
- The analytical methods were adequately described and validated.
- The supplier provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- The drug substance is packed in transparent polythene bag as primary and tied with nylon strip. Then placed in black color polythene bag as secondary and tied with nylon strip and finally placed in HDPE container with clamp.

- Stability of the API is submitted in accelerated (40°C±2°C /75% ± 5% RH) and long-term storage conditions (25°C ±2°C /60% ± 5% RH) and conclude the conformity of specifications during the shelf life and storage conditions. The retest period of the API is 60 months when stored below 25°C in the proposed container.

Drug Substance (Dapoxetine HCl)

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- Dapoxetine HCl is an off white to cream color powder. Dapoxetine HCl exhibits pH dependent solubility and has one chiral center. The active form is S-isomer. Dapoxetine HCl exhibits polymorphism, the manufacturing process adopted by the supplier produces the desired crystalline form A.
- The synthesis of drug substance includes five stages with the formation of four intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via mass spectrometry (MS), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR) and elemental analysis. Moreover, the crystalline form of Dapoxetine HCl has been confirmed by X-ray powder diffraction (XRD).
- The drug substance specifications include description, identification (IR), melting range, loss on drying, residue on ignition, specific optical rotation, related substances (HPLC), Enantiomeric purity, Acetic acid content (HPLC), triethylamine content (GC), assay (HPLC), residual solvents (GC), microbiological tests and particle size distribution.
- The analytical methods were adequately described and validated.
- The supplier provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- The API is packed in Transparent LDPE polythene bag as primary pack and tied with nylon strip. Then placed in black color LDPE polythene bag as secondary pack and tied with nylon strip and finally placed in HDPE container with clamp.
- Stability of the API is submitted in accelerated (40°C±2°C /75% ± 5% RH) and long-term storage conditions (25°C ±2°C /60% ± 5% RH) and conclude the conformity of specifications during the shelf life and storage conditions. The retest period of the API is 36 months when stored below 25°C in the proposed container.

Medicinal Product

- **Product Description**

-Oval yellow film coated tablet biconvex plain from one side and scored from the other side with white to off-white core.

-The product is packed in triplex PVC/PE/PVDC /ALU blister packs

-The excipients are Microcrystalline Cellulose pH 102, Calcium Hydrogen Phosphate, Lactose Anhydrous, Croscarmellose Sodium, Purified Talc, Colloidal Anhydrous Silica, Magnesium Stearate and Opadry TF titanium "yellow or equivalent"(Composed of Hypermellose, Macrogol/PEG, Calcium Carbonate, Iron Oxide Yellow, Talc 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 products of Sildenafil and Dapoxetine.

-Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**

-The manufacturing process consists of sieving, blending, lubrication, compaction, final blending, compression, coating and blistering.

-The manufacturing process has been adequately validated on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

- **Control of excipients**

-All excipients comply with Eur.Ph and USP except the Opadry TF titanium yellow which comply with in-house specifications.

- **Control of Drug Product**

-Product specifications include Description, Disintegration, Subdivision test, Mass Uniformity test, Water content (KF), identification (HPLC & UV), Assay (HPLC), Dissolution, Uniformity of dosage units, Related Substances (HPLC) and Microbiological tests.

-Analytical methods were revised and found to be suitable for the required testing.

-Batch Analysis from the proposed production site were provided for 3 commercial scale batches. The results of all tests are well within specification limits and batch data is acceptable.

- **Container closure system**

-The drug product is packed in triplex PVC/PE/PVDC /Alu blister then further placed in a carton box with an inner leaflet.

- **Stability**

-Stability of finished pharmaceutical product is submitted in accelerated (40°C ± 2 °C /75% RH ± 5% RH) and long-term (30°C ± 2 °C /65% RH ± 5% RH) storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The finished pharmaceutical product is stable for 24 months if stored below 30°C in a dry place. Additionally, the applicant submitted in use stability study for the half tablets for 10 days and the tests performed were in line with their acceptance criteria. Therefore, the subdivided dose is considered stable when stored at a temperature not exceeding 30̊C in a dry place for 10 days.

- **Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

-A declaration/certificate of TSE/BSE free is provided for the lactose anhydrous used in the manufacturing process of Virecta Plus scored film coated tablets. Moreover, the magnesium stearate used is from vegetable origin.

- **Summary basis of opinion:**

From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:
For the Drug substance (Sildenafil Citrate):

-XRPD diffractograms should be submitted for three batches to confirm the consistent formation of the desired crystalline form.

-Stability data for more recent batches covering the proposed retest period (60 months) should be submitted.

-Risk assessment of benzene, as a potential contaminant of the solvents used in the manufacturing process of sildenfil citrate, should be submitted.

For the Drug substance (Dapoxetine HCl):

-Results of the genotoxic impurities concluded from the risk assessment should be provided in at least 3 batches of the drug substances.

-The specifications of Dapoxetine HCl should be submitted on applicant letterhead including the test of particle size distribution

For the Drug product:

- A 2nd identification test for both APIs (Dapoxetine HCl & Sildenafil Citrate) should be considered as identification by a single chromatographic retention time procedure is not specific according to ICH Q6A guideline.

-The ability of the proposed analytical method of related substances to detect and quantify Sildenafil N-oxide impurity should be demonstrated.

The Quality of the drug product has been found satisfactory after

-The supplier of sildenafil citrate has provided XRD diffractograms for 3 batches of the drug substance confirming the consistent formation of the desired crystalline form.

-The supplier of sildenafil citrate has provided results of benzene in 3 commercial batches of the API and the results were far below the control threshold (0.6 ppm).

-The supplier of sildenafil citrate has provided stability data for more recent batches.

-The supplier of Dapoxetine HCl has provided results of genotoxic impurities in 3 drug substance batches and they were found below the detection limit.

-The applicant has provided the specifications of Dapoxetine HCl including the test of particle size distribution.

-The applicant has revised the specifications of the drug product to include 2nd identification tests for both APIs by UV spectroscopy.

-The applicant has proved the capability of the in house method to detect and quantify the N-oxide impurity as requested.

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

-Dapoxetine and sildenafil are a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
-Dapoxetine is indicated for treatment of premature ejaculation.
-Sildenafil is indicated for The treatment of erectile dysfunction in adult males and Pulmonary Hypertension

Pharmacokinetics

Bioequivalence Study

-The bioequivalence study of Virecta plus 60/100 mg FCT, manufactured by Eva Pharma, Egypt relative to Reference Products Priligy® 60 mg FCT Produced by Berlin-Chemie Menarini, Germany and Viagra® 100 mg FCT Produced by Pfizer administered to healthy participants.

Design

Open-label, Randomized, Single oral dose, Three-sequence, Three-period, Cross-over bioequivalence study in adult healthy adult male subjects under fasting conditions with a Washout Period of One week (7 days) Between periods in healthy participants.

Analytical Methods

-All procedures used to perform the bio-analyses of Dapoxetine and sildenafil 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 virecta plus 60/100 mg film coated tablets under fasting conditions.

Dapoxetine:

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	2621.878 ± 43.90	2919.579 ± 50.58	424.157 ± 36.97	1.979 (0.750-3.500)	17.342 ± 51.75
Reference (R1)	2779.725 ± 60.23	2885.553 ± 60.77	437.726 ± 38.95	1.865 (0.750-4.000)	16.402 ± 29.47
Reference (R2)	2648.061 ± 53.18	2746.447 ± 53.49	415.936 ± 42.66	1.854 (0.500-6.000)	14.777 ± 37.94
***Ratio (90%) CI**	(91.68- 106.91) 99.01%	(93.70- 115.21) 103.90%	(89.69- 109.50) 99.10 %		
CV (%)	18.41	24.93	24.05		

*ln-transformed values

Sildenafil

Treatment N=24	AUC0-t ng.h/ml	AUC0-∞ ng.h/ml	Cmax ng/ml	tmax h	t1/2 h
Test	1685.601 ± 40.27	1989.295 ± 78.25	381.878 ± 36.83	1.750 (0.500-3.500)	7.356 ± 180.56
Reference (R1)	1845.359 ± 41.30	1888.108 ± 41.09	413.507 ± 38.13	1.712 (0.333-3.000)	5.729 ± 61.63
Reference (R2)	1741.110 ± 39.83	1782.470 ± 40.33	388.048 ± 38.15	1.990 (0.750-6.000)	4.863 ± 36.82
***Ratio (90%) CI**	(87.03-100.64) 93.59%	(89.71-109.87) 99.28%	(85.63-105.30) 94.96%		
CV (%)	17.38	24.44	24.94		

*ln-transformed values

Conclusion

-The 90% confidence intervals calculated for AUC $_{0\text{-}t}$ and C $_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25.

-Based on this study demonstrated that the Dapoxetine and Sildenafil in virecta plus 60/100 mg Film Coated Tablets manufactured by EVA Pharma & reference products, Priligy® 60 mg FCT produced by Berlin Chemie Menarini, Germany and Viagra 100 mg FCT produced by Pfizer, Marketing Authorization Holder, Upjohn EESV, Netherlands are Bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 24 participants.