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)

Dablanca 20mg Film Coated Tablets

(Tadalafil)

Date: October 2023

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for "Dablanca 20mg Film Coated Tablets" from Ecophac for Pharmaceutical & Chemical Industries.

- The product contains the active substance "Tadalafil" which is reversible inhibitor of the cyclic guanosine monophosphate (cGMP) phosphodiesterase, PDE type 5 (PDE5), intended for the treatment of male erectile dysfunction.

II. Quality Aspect

Drug Substance

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

- The drug substance is white or almost white powder, practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride. Tadalafil has 2 chiral centers and therefore 4 stereoisomers may be found. The molecule obtained in the process described is in the **RR form**. Tadalafil exhibits polymorphism and the manufacturing process produces **Form I**.

- The synthesis of drug substance includes two synthetic steps with the formation of one intermediate. All starting materials, reagents, solvents are well controlled.

- The drug substance is elucidated via elemental analysis, infrared spectroscopy (IR), mass spectroscopy, H^1 NMR and C^{13} NMR, differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) and the structure is well characterized.

- The drug substance specifications are in accordance with USP and include the following tests: description, solubility, identification (IR, HPLC), loss on drying, residue on ignition, assay (HPLC), chromatographic purity (HPLC), enantiomeric and diastereomeric purity (HPLC), identification of polymorphic form (XRPD), residual solvents (GC), particle size and microbiological attributes.

- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of three drug substance batches demonstrating compliance with the current drug substance specification.
- Tadalafil is packed in food grade double polyethylene bags (primary packaging) then placed in fibre drums (secondary packaging) with proper sealing arrangements. Container closure system is suitable to store the API and comply with food grade packaging material and the specifications are acceptable.

- Stability of API is submitted accelerated storage conditions at 40°C±2°C / 75±5 %RH) and long-term storage conditions at (30°C±2°C/ 65±5%RH) and conclude the conformity of specifications during the shelf-life and storage conditions. Tadalafil should be stored at a temperature not exceeding 30 °C in cool place and protected from light.

Medicinal Product

- **Product Description:**
  - Golden round biconvex Film Coated Tablet
  - The product is packed in Carton box containing 1 or 2 or 3 (Aluminium/Transparent colourless PVDC) blisters each of 2 film coated tablet.
  - The excipients are Lactose monohydrate, Hydroxypropyl cellulose (Hyprolose), Sodium Lauryl Sulfate, Croscarmellose sodium, Microcrystalline cellulose (pH 102), Magnesium stearate, Colloidal Silicon Dioxide 200 (for tablet core) and Candurin Gold Sheen® "Titanium Dioxide, Potassium Aluiminium Silicate & Iron Oxide" (for film 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 consists of mixing, wet granulation, drying, lubrication, compression 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 Candurin Gold Sheen® and the specifications of the excipients are acceptable.
- Product specifications includes the four universal tests for description, identification (HPLC, IR), assay (HPLC), impurities (HPLC) and additional tests of mass uniformity, disintegration time, residual solvent (GC), dissolution of tadalafil by (HPLC), uniformity of dosage units (content uniformity) & microbiological tests. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for three 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 accelerated storage conditions at (40°C±2°C / 75±5 %RH) and long-term storage conditions at (30°C±2°C/ 65±5%RH) and concluded the conformity of

specifications during the shelf-life and storage conditions. Dablanca Film Coated Tablets should be stored at a temperature not exceeding 30°C in dry place.

- 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

Tadalafil is well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. Tadalafil is indicated for the treatment of erectile dysfunction in adults.

Tadalafil increase penile blood flow resulting from the relaxation of penile arteries & corpus cavernosal smooth muscle.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Dablanca 20mg Film Coated Tablets (Tadalafil 20mg) product of: Ecophac for Pharmaceutical & Chemical Industries, relative to the reference product Cialis 20mg Film Coated Tablets (Tadalafil 20mg) produced by: Lilly del Caribe Inc., Puerto Rico, released by: Lilly S.A. Avda De la Industria, Spain 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, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0, and 72.0 hours after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Tadalafil 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 **Tadalafil 20mg** under fast conditions.

Treatment N=28	**AUC0-t (ng.h/ml)**	**AUC0-inf (ng.h/ml)**	**Cmax (ng/ml)**	**tmax (h)**	**$T_{1/2}$ (h)**
Test	11202.07 ±3220.73	12827.42 ±3412.57	353.80± 103.83	4.04±2.57	23.74±2.85
Reference	11308.92±2919.82	12765.99±3209.00	392.34±122.92	3.57±2.61	23.41±3.81
***Ratio (90%) CI**	98.15 (91.55-105.23)	100.04 (94.04-106.42)	90.43 (81.15-100.77)	---------	----------

*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 Tadalafil 20mg in product dosage form of the test product Dablanca 20mg Film Coated Tablets (product of Ecophac for Pharmaceutical & Chemical Industries, Egypt) relative to the reference product Cialis 20mg Film Coated Tablets (Tadalafil 20mg) produced by: Lilly del Caribe Inc., Puerto Rico, released by: Lilly S.A. Avda De la Industria, Spain administered to healthy participants on 28 participants.