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)

Dalarectal 20mg Film Coated Tablets

(Tadalafil**)**

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 "Dalarectal 20 mg Film Coated Tablets" of Prime Pharma.

- 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. It is practically insoluble in water, freely soluble in dimethyl sulfoxide, slightly soluble in methylene chloride. Tadalafil has 2 chiral centers, so it is optically active, it is synthesized as R -enantiomer with (R) configuration, Tadalafil is non-hygroscopic and exhibits polymorphism and the manufacturing process produces **Form I**.
- The synthesis of drug substance includes 5 stages with formation of 4 intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, IR, ^{1}H-NMR, ^{13}C-NMR, X -ray powder diffraction and the structure is well characterized.
- The drug substance specifications are in accordance with Tadalafil monograph of the European Pharmacopeia and include the following tests: description, solubility, identification with IR & HPLC, specific optical rotation, XRD, loss on drying, sulfated ash, related substances, assay by HPLC, residual solvents, acetic acid content and particle size distribution test. All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specifications.
- Tadalafil is packed in a single white transparent low-density polyethylene (LDPE) bag sealed with plastic strip seal, the sealed bag is transferred in to black LDPE and sealed (Primary pack). HDPE containers are used for secondary packaging along with plastic seal. Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.
- Stability of API have been submitted on 3 production batches under long-term conditions (25°C/65% RH- simulated commercial packaging) and under accelerated conditions (40°C/75% RH- simulated commercial packaging) respectively and conclude the conformity of specifications during the shelf life and storage

conditions. The recommended storage conditions are "store at temperature not exceeding 25 °C, in a dry place".

Medicinal Product

- **Product Description**

- Dalarectal 20mg film coated tablets are "pale yellow to yellow round" biconvex non-scored film coated tablets with "white to off-white core".

-The product is packed in Aluminium /Transparent PVDC blisters, each of 2 film coated tablets.

-The excipients are: Lactose Monohydrate fine powder, Microcrystalline cellulose pH102, Hydroxypropyl Cellulose (HPC L.F), Croscarmellose sodium, Sodium lauryl sulfate, Magnesium stearate (for tablet core).and Hypromellose E15, Polyethylene Glycol 6000, Titanium Dioxide, Yellow Iron Oxide (for coating)

- **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 sieving, dry mixing, wet granulation, drying, blending, lubrication, compression, coating.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three primary batches.
- **Control of excipients**, all excipients comply with with USP except for Lactose Monohydrate Fine Powder, Sodium Lauryl Sulphate, Polyethylene Glycol 6000 which follow "B.P" specifications. the specifications of the excipients are acceptable.
- **Product specification** includes the four universal tests for description, identification (by HPLC & UV), assay, impurities and additional tests: uniformity of mass, disintegration time, dissolution rate, uniformity of dosage units, residual solvents & microbiological tests. All limits are acceptable.
- **Analytical methods** were adequately described and validated.
- **Batch Analysis** from the proposed production site were provided for 3 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 finished pharmaceutical product have been submitted on three primary batches under long-term conditions (30°C/65% RH -commercial packaging) and under accelerated conditions (40°C/75% RH-commercial packaging) respectively and conclude the conformity of specifications during the shelf-life and storage conditions. The recommended storage conditions are "To be stored at temperature not exceeding 30° C"

- 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 increases penile blood flow resulting from the relaxation of penile arteries & corpus cavernosal smooth muscle.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Dalarectal 20mg film coated tablets (product of Prime Pharma) relative to Cialis® 20mg film coated tablet form Lilly administered to healthy participants.

Design

A Comparative, Open-Label, Single Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, fasting, crossover bioequivalence study with a washout period of two weeks between periods in healthy participants.

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. 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 Dalarectal 20 mg film coated tablet and strength under fast condition.

Treatment N=31	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	T_{max} h	$t_{1/2}$ h
Test	8689.742	9875.480	388.134	2.330	18.566
Reference	8760.034	9938.588	374.447	2.670	19.140
*Ratio (90%) CI	99.455 (92.601- 106.817)	99.771 (92.639 -107.451)	104.556 (97.130 -112.54)	-------	--------
CV (%)			17.186	-------	------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 80 – 125%

Based on this study demonstrated that Tadalafil in the test product, Dalarectal 20 mg film coated tablet, (product of Prime Pharma) & reference product, Cialis® 20 mg film coated tablet form Lilly are bioequivalent after a single oral dose of test and reference administration under fasting conditions on 31 participants.