# EDA Assessment Report for human medicinal product

(Scientific Discussion)

## Tadatrona 5mg 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 Tadatrona 5 mg film coated tablets from Averroes pharma for pharmaceutical 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. Tadalafil has no effect in the absence of sexual stimulation.

# II. Quality Aspect

**Drug Substance**

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white powder, freely soluble in dimethyl sulfoxide, slightly soluble in methylene chloride and practically insoluble in water. It exhibits polymorphism (**Form I**) and it is RR- isomer.
- The synthesis of drug substance includes four steps within the formation of three intermediates. All starting materials, reagents, solvents and recovered solvents are well controlled. All critical steps and intermediates control are discussed.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, FTIR, $^{1}$H-NMR, $^{13}$C-NMR and the structure is well characterized. The polymorphism is confirmed via XRPD and DSC. The RR-isomer is controlled via specific optical rotation.
- The drug substance specifications are in accordance with USP and include the following tests description, solubility, identification (by IR, XRPD and HPLC), loss on drying, residue on ignition, enantiomeric and diastereomeric purity (by HPLC), chromatographic purity (by HPLC), assay (by HPLC), residual solvents and microbiological tests. All acceptance criteria are justified.
- All analytical procedures were adequately described and well validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specifications.
- The API is packed in double polyethylene (i.e. white in black) bags sealed with cable ties (Primary packing). The primary packing material is placed in an HDPE drum (Secondary packing). 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 (accelerated at 40°C±2°C / 75±5%RH and long term at 25°C±2°C / 60±5%RH) and conclude the conformity of specifications during the expiry period of 60 months and storage conditions. The storage conditions for Tadalafil are "Preserve in well-closed containers. Store at 25°C".

**Medicinal Product**

**Product Description**

- Tadatrona is bright yellow round biconvex film coated tablet plain from one side and contain AVS symbols from other side.
- The product is packed in strip of 7 tablets of opaque white PVDC and AL foil.
- The excipients are: lactose monohydrate, microcrystalline cellulose (Avicel PH 101), microcrystalline cellulose (Avicel PH 102), croscarmellose sodium, poloxamer, povidone, magnesium stearate. The coating ingredients are hypromellose (HPMC E5), polyethylene glycol 6000, titanium dioxide, talc and quinoline yellow.

**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 wet granulation, 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 quinoline yellow which is in house. The specifications of the excipients are well justified.

**Product specification**

- Product specification includes the four universal tests for description, identification (by HPLC-DAD), assay, impurities and additional tests including uniformity of mass, uniformity of dosage unit by content uniformity, disintegration, dissolution and microbial examination. All limits are acceptable.
- Analytical methods were adequately described and well validated.
- Batch Analysis from the proposed production site were provided 3 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, 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 Tadatrona 20mg film coated tablets (Tadalafil 20mg) manufactured by: Averroes pharma for Pharmaceutical Industries, relative to the reference product Cialis 20mg film coated tablets (Tadalafil 20mg) produced by: Eli Lilly Nederland B.V., The Netherland administered to healthy participants.

## Biowaiver

**The EDA was granted a biowaiver for the lower strength Tadatrona 5mg Film Coated Tablets based on the Bioequivalence Study of Tadatrona 20mg film coated tablets** for following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- both strengths of Tadalafil are manufactured by the same process.
- both tablets strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

## Conclusion

The Similarity factors for Test & Reference products are within acceptance range ($f2 \geq 50$).

Based on this study demonstrated that Tadalafil 5mg in product dosage form of the test product Tadatrona 5mg film coated tablets manufactured by: Averroes Pharma for Pharmaceutical Industries relative to the reference product are similar.

## Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Two-Sequence, Two Period, Crossover Bioequivalence Study with a Washout Period of two weeks 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 ,0.25,0.5,0.75,1,1.5,2,2.5,3,4, 5,6,8,12,36,48, 60 and 72. 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=25 | AUC0-t (ng.h/ml) | AUC0-inf (ng.h/ml) | Cmax (ng/ml) | tmax (h) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| **Test** | 8129.04194 ± 2256.675 | 9371.56091 ± 2878.169 | 282.82 ± 68.13 | 4 | 22.50 ± 7.84 |
| **Reference** | 8536.08506 ± 2479.367 | 9894.17149 ± 3493.122 | 324.08 ± 100.19 | 3 | 22.36 ± 7.44 |
| ***Ratio (90%) CI** | 94.5 % (88.16 %-101.3 %) | 94.66% (88.15 %-101.64%) | 89.14 % (80.14 %-99.15%) | -------- | ------- |

*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 Tadatrona 20mg Film Coated Tablets Manufactured by: Averroes Pharma for Pharmaceutical Industries.relative to The Reference Product Cialis 20mg Film Coated Tablets (Tadalafil 20mg) Produced by: Eli Lilly Nederland B.V., The Netherland administered to healthy participants on 25 participants.