EDA Assessment Report for human medicinal product

(Scientific Discussion)

Xtandi 40mg FCT

(Enzalutamide)

Date: June, 2025.

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Xtandi® 40mg Film coated tablets from Astellas Pharma International B.V. Scientific office.

The product is indicated for adult men with prostate cancer:

- That no longer responds to a hormone therapy or surgical treatment to lower testosterone.

or

- That has spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone

or

- Who had prior prostate removal or radiation and have rapidly rising PSA, but cancer has not spread to other parts of the body and responds to a hormone therapy to lower testosterone.

II. Quality Aspect

Drug Substance

- Full details of the S part have been submitted for evaluation.
- The drug substance is White to off-white solid, non-hygroscopic, freely soluble in 1-Methyl-2-pyrrolidone & acetonitrile, sparingly soluble in absolute ethanol & practically insoluble in aqueous solutions in different PH. Enzalutamide exhibits polymorphism where one crystalline form has been observed.
- The synthesis of drug substance involves three steps starting with commercially available raw materials. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via ^{1}H-NMR, ^{13}C-NMR, UV-spectroscopy, Mass Spectroscopy, IR-spectrometry and Elemental analysis.
- The drug substance specifications are Description, Identification (IR & HPLC), Assay (HPLC), Related substances (HPLC), Genotoxic impurities (GC), Residual solvents (GC) and Sulphated ash.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results that demonstrated compliance with the current drug substance specification.
- The drug substance is packed in double polyethylene bags with twist ties to close and further placed in Steel drums. The proposed Container closure system is suitable to store drug substance and comply with food grade packaging material and the specifications are acceptable

- Stability of drug substance is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 25°C ± 2°C, RH 60% ±5%), and conclude the conformity of specifications during the retest period of 48 months when stored at temperature not exceeding 25°C.

Medicinal Product

- **Product Description**

- Xtandi 40mg tablets are round, yellow film-coated tablets, debossed with E 40.

- The product is packed in Polyvinyl chloride laminated with polychlorotrifluoroethylene/aluminum foil blisters (PVC/PCTFE/Alu blisters).

- The excipients are: Hypromellose Acetate Succinate, Acetone, Cellulose Microcrystalline, Silica, Colloidal Anhydrous, Croscarmellose Sodium, Magnesium Stearate, OPADRY® Yellow & 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 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 preparation of spray-dried dispersion (SDD) followed by blending, dry granulation, final blending, compression, film coating & packaging.

- The manufacturing process was adequately validated according to relevant guidelines. Validation included 3 consecutive batches at the commercial production scale at the intended tablet manufacturing site.

- Control of excipients, all excipients comply with Ph. Eur. except for Hypromellose Acetate Succinate comply with NF specifications & OPADRY® Yellow which complies to In-house specifications.

- Product specification includes Description, Identification (HPLC/PDA), Assay (HPLC), Related substances (HPLC), Uniformity of dosage units (HPLC), Dissolution & Microbial tests.

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

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

- The film-coated tablets are packaged in polyvinyl chloride laminated with polychlorotrifluoroethylene /aluminum foil blisters (PVC/PCTFE/Alu blisters).

- Stability data was submitted in (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 30°C ± 2°C, RH 75% ±5%), and conclude the conformity of specifications during the shelf life and storage conditions. The finished pharmaceutical product is stable for 48 months if stored at temperature not exceeding 30°C.
- 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.

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:

-Carry over study of benzene to the final drug substance, as a contaminant from some of the solvents used in the manufacturing process, should be submitted.

For the Drug product:

-The control limits of impurity B and total impurities should be revised to be in line with EMEA public assessment report of Xtandi FCT according to the Reliance assessment pathway. Moreover, the available stability data in the climatic zone IV B (30°C/75%RH) at 48 months' time interval supports the more restricted limit.

The Quality of the drug substance has been found satisfactory after:

-The drug substance`s supplier has provided results of benzene in multiple batches of the drug substances and the results were consistently below the detection limit.

The Quality of the drug product has been found satisfactory after:

-The Finished pharmaceutical products`s manufacturer has revised the control limit of impurity B and the total impurities as requested to be in line with EMEA public assessment report of Xtandi FCT.

Recommendation

-Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved.

III. Non-Clinical& Clinical Aspects

-Introduction

Enzalutamide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Enzalutamide is indicated for the treatment of castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer (mCSPC), and non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR).

-Mechanism of action

Enzalutamide is a competitive androgen receptor (AR) inhibitor that has a threefold inhibition on the androgen signaling pathway without significant AR agonist activity.9,1 It inhibits androgen binding to its receptor, androgen receptor nuclear translocation, and subsequent interaction with chromosomal DNA to upregulate oncogenes.1,2 Enzalutamide binds to the AR with 5 to 8-fold greater affinity than first-generation antiandrogens such as bicalutamide and only 2-3 fold reduced affinity than the natural ligand dihydrotestosterone.3 Molecular docking showed that enzalutamide binds to the ligand binding domain of the AR distinctive from that of bicalutamide.

- Summary of Listing of Clinical Studies:

*** Efficacy, PK and Safety Studies**

1-CRPC2 (AFFIRM) North America, South America, Europe, Australia, South Africa "Phase 3, multicenter, randomized, double-blind, placebo-control".
2- 9785-CL-0232 (Asian PREVAIL) "Phase 3, multicenter, randomized, double-blind, placebo-control".
3- MDV3100-03 (PREVAIL) "Phase 3, Multinational, Randomized, Double-Blind, Placebo-Control".
4- MDV3100-14 (PROSPER) North America, South America, Europe, Australia, Asia "Phase 3, multicenter, randomized, double-blind, placebo-control".
5- 9785-CL-0335 (ARCHES) North America, South America, Europe, Middle East, Australia/New Zealand, Asia "phase 3, multicenter, randomized, double-blind, placebo-control".
6- MDV3100-13 (EMBARK) North America, South America, Europe, Australia, Asia "Phase 3, multicenter, randomized, double blind, placebo control (enzalutamide + leuprolide; placebo + leuprolide) and open-label (enzalutamide monotherapy).

Based on the clinical study Xtandi 40mg FCT submitted to EDA, found to recommend the approval of the marketing authorization of product.