EDA Assessment Report for human medicinal product

(Scientific Discussion)

Nat- abiraterone 250mg Tablets

(Abiraterone)

Date: December 2024

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for NAT- Abiraterone Tablet from SEDICO.
- The product is indicated as a CYP17 inhibitor mainly indicated for use in combination with prednisone for the treatment of patients with metastatic prostate cancer who have received prior chemotherapy containing docetaxel.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to off-white powder. Freely soluble in methylene chloride, in tetrahydrofuran and in toluene, soluble in ethyl acetate, in isobutyl methyl ketone, in N, N- dimethyl formamide and in acetone, sparingly soluble in acetonitrile and in dimethyl sulfoxide, slightly soluble in hexane, very slightly soluble in 0.1 N hydrochloride, practically insoluble in water. It exhibits polymorphism.
- 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 IR, UV, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy, Elemental Analysis, X-ray powder diffraction (XRPD) & thermal analysis and the structure is well characterized.
- The drug substance specifications are description, solubility, identification (by IR & HPLC), water content, specific optical rotation, residue on ignition, assay (HPLC), related substances (HPLC), residual solvents (HS-GC), palladium content (ICP-MS) & PSD. 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 specification.
- Container closure system is first packed in clear low-density polyethylene (LDPE) bag (primary packaging material), tied either using thread or strip. It is inserted in a black colored LDPE bag and tie bag either using thread or strip. Place this bag in triple laminated bag and seal it. Place this bag in suitable HDPE drum and seal the drum. Container closure system is suitable to store drug substance and comply with food grade packaging material and the specifications are acceptable

- Stability of API 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 and storage conditions.

Medicinal Product

Product Description

- NAT-Abiraterone 250mg is White to off-white colored, oval shaped, tablets debossed with 'NA250' on one side and plain on other side.
- The product is packed in 150cc HDPE bottles with 38mm CR closures. The packaging materials used in the packaging of Abiraterone Acetate tablets, 250 mg are inert and are commonly used for oral drug products
- The excipients are: Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Povidone (K-30), Sodium lauryl sulphate, Magnesium Stearate, Colloidal Silicon dioxide & 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 wet granulation, drying, milling, lubrication, compression & blistering.
- The manufacturing process was adequately validated according to relevant guidelines from three commercial batches.
- Control of excipients, all excipients comply with USP except for purified water which complies with in-house specifications
- Product specification includes description, identification (HPLC & UV), uniformity of dosage units by weight variation, water content, dissolution (HPLC), assay (HPLC), related substances (HPLC) & microbiological tests.
- Analytical methods were were revised and found to be suitable for the required testing.
- Batch Analysis from the proposed production site were provided for 5 batches. The results of all tests are well within specification limits and batch data is acceptable.

- Stability of finished pharmaceutical product is submitted and conclude the conformity of specifications during the shelf life and storage conditions. The finished pharmaceutical product is stable for 36 months if stored below 30°C.
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, there are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product except for Lactose monohydrate for which certificate of TSE/BSE free is provided.

Summary basis of opinion:

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

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

Abiraterone is indicated as an anti-tumor hormone therapy used for the treatment of certain types of prostate cancer.

Mechanism of Action:

Abiraterone is a potent, irreversible, and selective inhibitor of 17 αhydroxylase/C17,20-lyase (CYP17), an enzyme expressed in testicular, adrenal, and prostatic tumour tissues, to regulate androgen biosynthesis. It is used to treat metastatic castration-resistant prostate cancer and hormone-sensitive high-risk metastatic prostate cancer.

As abiraterone has poor oral bioavailability and is susceptible to hydrolysis by esterases, abiraterone acetate was developed as an orally bioavailable prodrug with enhanced stability and absorption.

Pharmacokinetics:

Following oral administration of abiraterone acetate to patients with metastatic castration-resistant prostate cancer, the median Tmax was two hours. *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies of other abiraterone acetate formulations, abiraterone acetate plasma concentrations were

below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Bioequivalence Study:

The bioequivalence study of Nat-abiraterone 250mg Tablets from SEDICO& Zytiga® Tablets 250 mg from Janssen Inc., Toronto, Ontario.

Study Design:

This study was a double blind, balanced, randomized, three-sequence, two-treatment, three-period, single oral dose, partial reference replicate, bioequivalence study in normal, healthy, adult, human male subjects under fasting condition. A washout period of 07 days was maintained between the dosing days of any two consecutive periods.

Criteria for evaluation:

Pharmacokinetic:

For pharmacokinetic evaluations, a total of 22 blood samples were collected in each period at the time points specified in the protocol. Standard non-compartmental of Phoenix® WinNonlin® Version 6.4 (Certara L.P.) was used to derive pharmacokinetic parameters for Abiraterone.

Safety:

Safety was assessed from the screening period to the end of the study. It was assessed through clinical examination, vital signs assessment, oral body temperature, 12-lead electrocardiogram (ECG), chest X-ray (posterior-anterior view), clinical laboratory parameters (e.g. hematology, biochemistry, urine analysis and immunology), subjective symptomatology and monitoring of adverse events.

Statistical methods:

Descriptive statistics are calculated and reported for all pharmacokinetic parameters of Abiraterone.

The within-subject standard deviation of reference product (S_{WR}) are calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_T and AUC_I for Abiraterone.

ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters C_{max}, AUC_T and AUC_I are calculated and reported for Abiraterone.

Using two-one sided tests for bioequivalence, 90% confidence intervals for the ratio of the geometric least squares means between drug formulations are calculated for ln-transformed data of C_{max}, AUC_T and AUC_I for Abiraterone.

Criteria for conclusion of bioavailability evaluation are as follows:

The following comparative bioavailability standards will need to be applied on data of Abiraterone:

1. The 90% confidence interval of the relative geometric LSmean AUC_T of the test to reference product should be within the following limits:

a. 80.0%-125.0%, if $S_{WR} \leq 0.294$ (i.e., CV ≤ 30.0%),

b. $[\exp(-0.76 S_{WR}) \times 100.0\%]$-$[\exp(0.76 S_{WR}) \times 100.0\%]$ if $0.294 < S_{WR} \leq 0.534$ (i.e.,30.0% < CV ≤ 57.40%), or

c. 66.7% -150.0%, if $S_{WR} > 0.534$ (i.e., CV > 57.4%);

2. The relative geometric LSmean AUC_T of the test to reference product should be within 80.0% and 125.0% inclusive;

3. The relative geometric LSmean maximum concentration (C_{max}) of the test to reference product should be within 80.0% and 125.0% inclusive.

The measured drug content of the lots of the test and reference products used in the study (expressed as percent of label claim) was within 5% of each other. Hence, the study results and conclusion are presented with potency uncorrected data only.

The pharmacokinetic parameters of Abiraterone for Test Product-T and Reference Product-R are summarized in the following table:

Descriptive Statistics of Formulation Means for Abiraterone (N = 60)

Parameters (Units)	Test Product-T (N = 60 Observations)	Reference Product-R (N = 117 Observations)
Tmax (h)#	2.250 (1.000 - 10.000)	2.000 (1.000 - 5.017)
Cmax (ng/mL)	28.349 ± 17.1975	23.898 ± 14.6669
AUCT (ng.h/mL)	158.440 ± 87.4216	137.392 ± 82.4870
AUCI (ng.h/mL)	164.251 ± 88.0023	143.468 ± 82.9607
λz (1/h)	0.078 ± 0.0325	0.078 ± 0.0338
TLIN (h)#	10.000 (2.500 - 24.000)	10.000 (1.500 - 36.050)
LQCT (h)#	36.000 (12.000 - 72.083)	36.000 (12.000 - 72.000)
t½ (h)	9.724 ± 2.3800	9.875 ± 2.8427
AUCT/AUCI (%)	95.432 ± 2.8777	94.414 ± 4.3432
Tlag (h)#	0.000 (0.000 - 1.250)	0.000 (0.000 - 0.517)

Within-Subject Standard Deviation of Reference Product (S_{WR}) and intra subject CV of Reference Product-R for Abiraterone (N = 59)

Dependent	lnCmax	lnAUCT	lnAUCI
Within-Subject Standard Deviation of Reference Product (S_{WR})	0.3349	0.2605	0.2457
Intra Subject CV of Reference Product- R (%)	34.5	26.5	24.9

Relative Bioavailability Results for Abiraterone (N = 60)

	Geometric Least Squares Means					
Parameters	**test Product- (N = 60 Observations)**	**Reference Product-R (N = 117 Observations)**	**Ratio (T/R) %**	**90% Confidence Interval**	**Acceptance Criteria**	**Power (%)**
$\ln C_{max}$	23.480	19.800	118.6	109.1 - 128.9		99.6
$\ln AUC_I$	134.858	115.331	116.9	109.6 - 124.8	80.0 - 125.0	100.0
$\ln AUC_I$	141.422	122.272	115.7	108.6 - 123.1		100.0

Conclusion:

The sponsor provided data obtained following the administration of Nat-Abiraterone tablets and Zytiga® Tablets (Abiraterone acetate) (Janssen Inc., Canada), administered as 250 mg in a randomized, two-treatment, three- period, reference replicated crossover comparative bioavailability study conducted in healthy subjects under fasting conditions. Pharmacokinetic parameters and statistical data calculated by the sponsor are in agreement with those calculated by the reviewer.
The ratios of mean AUCT/AUCI for both the test and reference products are above 80%.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, and are within the bioequivalence acceptance range of 80-125% are within the bioequivalence acceptance range & accept scaling up acceptance range according to high variability of Abiraterone for Cmax parameter (based on Within-Subject Standard Deviation of Reference Product (SWR) and intra subject CV of Reference Product-R for Abiraterone).

Based on this study demonstrated that the Active Pharmaceutical Ingredient Abiraterone in Nat-Abiraterone tablets from SEDICO & Zytiga Tablets (Abiraterone acetate) (Janssen Inc., Canada), are Bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 60 participants.