EDA Assessment Report for human medicinal product

(Scientific Discussion)

NAT-Gefitinib 250mg Film Coated Tablets

(Gefitinib)

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-Gefitinib Tablet from SEDICO.
- The product is indicated as the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

II. Quality Aspects

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white crystalline powder, Practically insoluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane. It exhibits polymorphism.
- The synthesis of drug substance includes four stages with the formation of three intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR, UV, ^{1}H-NMR, P-XRD, ^{13}C-NMR, Mass spectroscopy & Elemental Analysis and the structure is well characterized.
- The drug substance specifications are description, solubility, identification (by IR, HPLC & P-XRD), water content, sulphated ash, assay (HPLC), related substances (HPLC), residual solvents (HS-GC & HPLC) & 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 colorless low-density polyethylene (LDPE) bag (primary packaging material), securely folded and tied with a yellow cable tie (strip seal) having NATCO logo. It is inserted in a black colored LDPE bag. The open end is folded and tied with white cable tie (strip seal) having NATCO logo. These two bags are then put into HDPE drum. Blue colored, cylindrical HDPE drums with screw lid, reinforced with metallic clamp are used for packing. The drum is sealed with “Double security seal” (green colored tamper-proof two-piece seal with NATCO logo and having a control serial number). The product label is pasted on the HDPE drum. One additional product label is also pasted on the inner side of 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 30°C ± 2°C, RH 75% ±5%), and conclude the conformity of specifications during the retest period and storage conditions.

Medicinal Product

- **Product Description**

  NAT-Gefitinib 250mg is Brown colored, round shaped, film coated tablets debossed with 'N' on one side and '250' on other side.

- The product is packed in Blister of 10 tablets, such three blisters packed in aluminum pouch. The packaging materials used in the packaging of Gefitinib tablets, 250 mg are inert and are commonly used for oral drug products
- The excipients are:
  - Tablet core (Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Povidone (K-30), Sodium lauryl sulphate, Magnesium Stearate & Purified water)
  - Tablet coating (Opadry II 85F565188 Brown & 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 sifting, dry mixing, wet granulation, drying, blending, pre-lubrication, lubrication, compression, film coating & 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 the coating material which complies with in-house specifications.
- Product specification includes description, identification (HPLC-PDA), uniformity of dosage units by weight variation, water content, average weight per tablet, dissolution (HPLC), assay (HPLC), Degradation Products (HPLC) & Microbial Enumeration test.
- Analytical methods were were revised and found to be suitable for the required testing.
- Batch Analysis from the proposed production site were provided for 3 batches. The results of all tests are well within specification limits and batch data is acceptable

- Container closure system is Blister (Triplex film PVC/PE/PVDC -Plain aluminum foil) of 10 tablets, such three blisters packed in aluminum pouch
- 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:
From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:
For the Drug product:
- The absence of aluminum pouch from the description of the Container Closure System although it is clarified in the stability section as the pack on which the stability studies were performed
- The control of "3-Chloro-4-Fluoro Aniline" under "any unspecified impurities" is not clarified in the section of drug product specifications
-The absence of Elemental impurities risk assessment according to ICH Q3D

The Quality of the drug product has been found satisfactory after:
- The applicant added the aluminum pouch to the description of the Container Closure System.
-The applicant added a footnote below the table of drug product specifications that the control of "3-Chloro-4-Fluoro Aniline" is under "any unspecified impurities".
- The applicant submitted the Elemental impurities risk assessment according to ICH Q3D

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

-Indication: Gefitinib is indicated as the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Pharmacokinetics

Bioequivalence Study

-An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Three-Sequence, Three-Period, Partial Replicate Bioequivalence Study of Gefitinib Tablets, 250 mg from SEDICO and IRESSA (Gefitinib) Tablets 250 mg of AstraZeneca Pharmaceuticals LP Wilmington, in Healthy, Adult, Human Male Subjects under Fasting Conditions.

Design

-Single-Dose, Two-Treatment, Three-Sequence, Three-Period, Partial Replicate Bioequivalence Study with a washout Period of 14 days Between periods in healthy participants.

Analytical Methods

-All procedures used to perform the bio-analyses of Gefitinib 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:

- **For Gefitinib**:

	Arithmetic Mean ± SD (%CV)	
Pharmacokinetic Parameters (Units)	**Reference Product (R) (N = 105)**	**Test Product (T) (N = 53)**
Cmax (ng/mL) 192.225 ± 74.1096 (38.55%) Tmax (hr)	**192.225 ± 74.1096 (38.55%) 5.750 (1.50 - 12.00)**	**186.343 ± 75.2630 (40.39%) 5.750 (2.50 - 24.00)**
AUC0-t (hr*ng/mL)	**5982.284 ± 2531.1349 (42.31%)**	**5799.883 ± 2305.9053 (39.76%)**
AUC0-∞ (hr*ng/mL)	**6643.379 ± 3058.7156 (46.04%)**	**6376.254 ± 2707.7795 (42.47%)**
t½ (1/hr)	**33.179 ± 11.4436 (34.49%)**	**32.836 ± 10.6493 (32.43%)**
Kel (hr)	**0.025 ± 0.0133 (53.93%)**	**0.024 ± 0.0108 (44.74%)**
AUC_%Extrap_obs (%)	**8.520 ± 5.4851 (64.38%)**	**8.255 ± 5.1854 (62.82%)**

* A total of 54 healthy adult were enrolled in the study as per protocol:
Following subjects were withdrawn during the conduct of the study:
- Subject no. 27 was withdrawn from the study due to an adverse event during period 1.
- Subject no. 53 was withdrawn from the study due to drug abuse test during admission of period 3, hence withdrawn from period 3. Hence, total of 53 subject completed the study.
-A total of 54 subjects were enrolled in the study and 52 subjects completed all the periods of the study. However Pharmacokinetic and statistical analyses were performed over 53 subjects who completed at least two

periods of the study as per the approved protocol. Subject no. 53 completed two periods with one test and one reference product hence included in the statistical analysis using conventional average bioequivalence approach. Hence, total of 53 subject completed the study.

-The results For Gefitinib using Conventional Average Bioequivalence Approach for C_{max} submitted for information purpose as follows:

Pharmacokinetic Parameters (Units)	Geometric Least Squares Means And its Ratio Test Product (T) (N=53)	Geometric Least Squares Means And its Ratio Reference Product (R) (N=105)	Geometric Least Squares Means And its Ratio (T/R) %	Intra-subject CV of Reference Product (%)	90% Confidence Interval
Cmax (ng/mL)	167.947	177.256	94.75	34.11	87.76% - 102.29%
AUC0-t (hr*ng/mL)	5272.607	5409.700	97.47	27.04	91.43% - 103.90%
AUC0-∞ (hr*ng/mL)	5756.975	5921.110	97.23	26.80	91.16% - 103.70%

Conclusion

-The 90% confidence intervals calculated for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25.

-Based on this study demonstrated that the NAT-Gefitinib 250mg Film Coated Tablets (Gefitinib), from SEDICO & IRESSA (Gefitinib) Tablets 250 mg of AstraZeneca Pharmaceuticals LP Wilmington are Bioequivalent after a single oral dose of test and reference administration under Fasting on healthy participants.