EDA Assessment Report for human medicinal product

(Scientific Discussion)

Imaten 100 mg & 400 mg Film Coated Tablet

Imatinib (as Mesylate)

Date: February, 2026.

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Imaten 100 mg & 400 mg Film Coated Tablets from ELIXIR PHARMA-Egypt

The product is indicated for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

II. Quality Aspect

Drug Substance

- A CEP has been submitted for evaluation.
- The drug substance is off-white to brownish yellow colour powder. Imatinib is freely soluble in water, slightly soluble in ethanol (96 per cent), Practically insoluble in methyl chloride. Imatinib Mesylate exhibits polymorphism. The polymorph for Imatinib Mesylate produced by the supplier is Form-α. Imatinib Mesylate does not contain any chiral centres. It does not exhibit isomerism.
- The drug substance specifications are Description, Solubility, Identification by Infrared absorption and XRD, Water content by KF, Sulphated ash, Related substances (HPLC), Impurity-F content (LC-MS/MS), impurity-H content (HPLC), Assay (HPLC) and Residual solvents (GC), Microbiological examination and Particle size (By laser diffraction).
- Analytical methods are in line with the current version of the European pharmacopeia monograph and the certificate of suitability (CEP).
- The applicant provided batch analysis results of 3 batches. The results of all tests were well within specification limits and batch data was found acceptable.
- As per the CEP issued by the EDQM regarding the container closure system, the substance is packed in a polyethylene under nitrogen in a triple laminated bag, placed in a polyethylene drum with silica gel bags in between.
- The retest period of the drug substance is 60 months when preserved in tight, light-resistant containers and stored at 25°C.

Medicinal Product

- **Product Description**

-Imaten 100 mg film-coated tablets: White to off-white colored, round, bevel edged scored tablets debossed with H on one side and 19 on the other side, 1 and 9 separated by a score line.
-Imaten 400 mg film-coated tablets: White to off-white colored, capsule shaped, bevel edged scored, film-coated tablets debossed with H on one side and 20 on the other side, 2 and 0 separated by a score line.

-The product is packed in carton box, each carton box contains 3 Al/Al ((Soft forming aluminum foil (OPA/Alu/PVC) and hard lidding aluminum foil blister) blisters, each blister of 10 film coated tablets.

-The excipients are Imatinib mesylate, Magnesium stearate and Opadry white (composed of Hypromellose, Titanium dioxide, Macrogol / PEG (MW 8000) and Talc).

- **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 & Blending/Lubrication, Compression, Coating and blistering.

-The manufacturing process has been adequately validated on three full production scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

- **Control of excipients**

-All excipients comply with European Pharmacopeia except for Opadry white which complies with in house specifications.

- **Control of drug product**

-Product specification includes Description, Identification (HPLC & UV), Average weight (mass), Water content (KF), Subdivision test, Dissolution (UV), Uniformity of dosage units, Related Compounds (HPLC), Related Compounds (LCMS), Assay (HPLC), Microbiological examination and Residual solvents (GC).

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

-Batch Analysis from the proposed production site were provided for 2 commercial batches of each strength. The results of all tests are well within specification limits and batch data is acceptable

- **Container closure system**

-The drug product is packed in a blister formed using Lidding foil of 141 mm, Plain aluminum foil (Hard Tempered) (25 µ aluminum foil with 7GSM HSL coating on bright side) and forming foil of 141mm cold form foil (60 microns PVC / 45 microns aluminum foil/ 25 microns OPA). The blisters are then placed in a carton box with an inner leaflet.

- **Stability**

-Stability of finished pharmaceutical product is submitted in accelerated (40°C ± 2 °C /75% RH ± 5% RH) and long-term (25°C/60% RH & 30°C/75% RH) storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The finished pharmaceutical product is stable for 24 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, 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:
-A written commitment that the applicant will inform EDA in the event that the CEP is revised, renewed or withdrawn by EDQM should be submitted

For the Drug product:

-Discussion of the developmental trials carried out for optimization of the formulation till the final formula has been obtained should be submitted.
-The subsection of characterization of impurities should be revised to include a discussion of the specified impurities controlled in the specifications clarifying their structures, chemical names, origin and control strategy

The Quality of the drug product has been found satisfactory after

-The applicant has submitted a written commitment stating EDA will be informed in the event that the CEP is revised, renewed or withdrawn by EDQM.
-The manufacturer has submitted discussion of the developmental trial carried out for optimization of the formulation.
-The manufacturer has updated the characterization of impurities subsection to include the required

discussion of the specified impurities with a clarification of their structures, chemical names, origin and control strategy.

- **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**

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

Imatinib (as Mesylate) is indicated for:

1-In adult and pediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
2- In adult and pediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
3- In adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
4- In adult patients with relapsed or refractory Ph+ ALL as monotherapy.
5- In adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements
6- In adult patients with advanced hyper eosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.
7- In treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
8- In the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST.

- **Pharmacokinetics**

Bioequivalence Study

-The bioequivalence study was conducted for Imaten 400mg Film Coated Tablet (Imatinib Mesylate eq. to 400mg) from Elixir Pharma-Egypt relative to Glivec® 400mg Tablet (Imatinib 400 mg), administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Imatinib 100 mg Film Coated Tablet from Elixir Pharma-Egypt based on the following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- All strengths of Imatinib are manufactured by the same process.
- Imatinib has linear pharmacokinetics over the therapeutic dose range.
- All tablets strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

-An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of test product (Imatinib 400 mg Tablets, manufactured by: Hetero Labs Ltd., India) from Elixir Pharma-Egypt in comparison with reference product Glivec® (Imatinib) 400 mg Tablets, Manufactured by: Novartis Europharm Limited, with a Washout Period of 8 days Between 2 periods in in healthy, adult, human male subjects under fed condition.

Analytical Methods

-All procedures used to perform the bio-analyses of Imatinib 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 Product name and strength under fed conditions.

Treatment N=35	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	35209.652 ± 11864.6972	36877.054 ± 12685.6667	1863.516 ± 597.8907	3.000	15.639 ± 3.0747
Reference	34795.946 ± 12311.5359	36499.566± 13134.5348	1877.598 ± 624.9066	3.667	15.091 ± 3.0018
***Ratio (90%) CI**	102.1 (97.15 – 107.33)	102.0 (97.09 – 107.14)	99.4 (93.67 – 105.41)	NA	NA
CV (%)	12	11.8	14.7	NA	NA

*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 Imatinib 400 mg Tablets, from Elixir Pharma-Egypt Relative To reference product Glivec® (Imatinib) 400 mg Tablets, manufactured by: Novartis Europharm Limited are Bioequivalent after a single oral dose of test and reference administration under Fed conditions on 35 participants.