EDA Assessment Report for human medicinal product

(Scientific Discussion)

Fumarox 120mg and 240 mg Delayed Release Capsule

(Dimethyl Fumarate)

Date: March, 2025.

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Fumarox 120mg and 240 mg from ELIXIR PHARMA-Egypt.

-The product is indicated for the treatment of adult and pediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is a white to off-white powder, non-hygroscopic, slightly soluble in dimethylformamide. Dimethyl fumarate does not exhibit isomerism, due to absence of chiral centers. Dimethyl fumarate exhibits polymorphism and the polymorphic form resulting from the manufacturing process is Form I.
- The synthesis of drug substance includes two stages. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via H-NMR-, UV-spectroscopy, MS, IR-spectrometry, X-ray powder diffraction, Elemental analysis, Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA).
- The drug substance specifications are description, solubility, identification (by IR, HPLC & P-XRD), water content, residue on ignition, heavy metals, fumaric acid content (HPLC), particle size, assay (HPLC), related substances (HPLC), residual solvents (GC) and microbiological tests. 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.
- The drug substance is packed in double polythene bag (white in black), and both bags are tied with fastener (individually) and further placed in HDPE 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 of 60 months when stored at 25°C with excursions permitted between 15°C and 30°C.

Medicinal Product

- **Product Description**

- Fumarox 120 mg: Light blue opaque size '0' hard gelatin capsules imprinted with 'H' on cap and 'D12' on body filled with white to off white tablets.

- Fumarox 240 mg: White opaque size '0el' hard gelatin capsules imprinted with 'H' on cap and 'D15' on body filled with white to off white tablets.

-The product is packed in (Alu /triplex clear PVC/PE/PVDC) blister of 10 delayed release Capsules then placed in a carton box.

-The excipients are: Silicified microcrystalline cellulose, Croscarmellose sodium, Talc, Colloidal silicon dioxide, Magnesium stearate, Opadry enteric white 94O580021, Polysorbate 80, Isopropyl alcohol, Purified water, Acryl EZE II white 493Z180022 and Triethyl citrate.

- **Pharmaceutical development**

-The development of the product has been described, the aim was to develop a delayed release formulation equivalent to the reference product that prevents release of the active ingredient in the gastric environment while allowing for rapid release of the active ingredient in the intestine region. The choice of excipients is justified and their functions explained.

-Overall, the choices of the packaging, manufacturing process, physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**

-The manufacturing process consists of sifting, blending and sifting, pre-lubrication/lubrication, compression, preparation of primary coating suspension, secondary coating, capsule filling and packing.

-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.

- **Control of drug product**

- The specifications include the following tests: description, identification (HPLC-UV), average weight of filled capsule, average net fill content, lock length, water content, uniformity of dosage units by weight variation, dissolution (HPLC), assay (HPLC), Degradation Products (HPLC), residual solvents (GC) and Microbial Enumeration test.
-Analytical methods were revised and found to be suitable for the required testing.
-Batch Analysis results from the proposed production site were provided for 6 batches (3 batches foreach 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 (Alu /triplex clear PVC/PE/PVDC) blister of 10 delayed release Capsules with package insert and Patient information in a carton box.

- **Stability**

-Stability data of 6 batches (3 batches for each strength) 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 24 months if stored below 30°C, protect from light.

- **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 magnesium stearate and gelatin present in the hard gelatin capsules. A declaration/certificate of TSE/BSE free is submitted for magnesium stearate and hard gelatin capsules used in Fumarox 120 mg and 240 mg Delayed Release Capsule.

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:
- The control of Microbiological testing is not clarified in the section of drug substance specifications.
- The solubility of drug substance in water and other solvents should be submitted.
- The absence of Evaluation report which confirm no possible Genotoxic impurities.
- There's a possibility for the formation of Methyl hydrogen fumarate during the synthetic process. Therefore, the control strategy taken to prevent its carryover to the final API should be clarified.

For the Drug product:
-The control of "Fumaric acid impurity" under "any unspecified impurities" is not clarified in the section of drug product specifications.
-Elemental impurities risk assessment according to ICH Q3D should be submitted

The Quality of the drug substance has been found satisfactory after:
-The drug substance manufacturer submitted results of microbiological testing for multiple batches justifying the omission of microbiological testing in the upcoming batches according to ICH Q6A decision tree #6.
- The drug substance manufacturer submitted complete report of solubility of drug substance in water and other solvents.
- The drug substance manufacturer submitted Genotoxic impurities evaluation report.
- The drug substance manufacturer submitted the results of monomethyl fumarate (MMF) and monomethyl maleate (MMM) in multiple batches of dimethyl fumarate and they were consistently below the detection limit.

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

-The applicant added a footnote below the table of drug product specifications that the control of "Fumaric acid impurity" is under "any unspecified impurities".

- The applicant submitted the Elemental impurities risk assessment according to ICH Q3D.

Recommendation:

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

III. Non-Clinical& IV. Clinical Aspects

Introduction

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

Dimethyl Fumarate is indicated for the treatment of relapsing forms of multiple sclerosis, clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The mechanism of action of dimethyl fumarate in multiple sclerosis is not well understood. It is thought to involve dimethyl fumarate degradation to its active metabolite monomethyl fumarate (MMF) then MMF up-regulates the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway that is activated in response to oxidative stress.

Pharmacokinetics

-Once ingested, dimethyl fumarate is rapidly hydrolyzed by esterases to form monomethyl fumarate (MMF). Therefore, there is a negligible amount of dimethyl fumarate in the body, and all pharmacokinetic information is quantified with MMF. The time to maximum concentration (tmax) of MMF ranges between 2 and 2.5 hours. In patients with multiple sclerosis given 240 mg of dimethyl fumarate two times a day with food, the Cmax and AUC were 1.87 mg/L and 8.21 mg·hr/L, respectively. High-fat, high-calorie meals decrease the Cmax of MMF by 40% and cause a tmax delay from 2 hours to 5.5 hours; however, these changes are not considered clinically significant

Bioequivalence Study

The bioequivalence study of Fumarox 240mg Delayed Release Capsules from ELIXIR PHARMA-Egypt was done relative to Tecfidera® 240mg Delayed Release Capsules of Biogen Inc. Cambridge administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Fumarox 120mg Delayed-Release Capsules based on the following arguments:

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

Design

The Study was an open-label, balanced, randomized, two-treatment, two-sequence, four-period, single oral dose, fully replicate crossover bioequivalence study of Fumarox 240mg Delayed Release Capsules from ELIXIR PHARMA-Egypt with Tecfidera® (dimethyl fumarate) Delayed Release Capsules 240 mg of Biogen Inc. Cambridge, in normal, healthy, adult human subjects under fast & fed condition.

Biological Samples Collection;

Pre-dose, 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 56.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00 and 24.00 hours post dose administration.

Analytical Methods

-All procedures used to perform the bio-analyses of dimethyl fumarate name 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 Monomethyl Fumarate (MMF) of Fumarox 240mg Delayed release Tablet under Fed conditions.

Treatment N=45	AUC0-t ng.h/ml	AUC0-∞ ng.h/ml	Cmax ng/ml	tmax h	t1/2 h
Test	3319.97 ± 784.31 (23.62)	4379.38 ± 1879.78 (42.92)^	1816.35 ± 584.46 (32.18)	5.84 (3.42 – 12.00)	2.50 ± 3.48
Reference	3684.10 ± 717.13 (19.47)	3997.48 ± 837.22 (20.94)#	1899.89 ± 607.79 (31.99)	5.67 (3.50 – 12.00)	1.24 ± 0.74
*Ratio (90%) CI	(85.42-93.21) 100	(92.72-108.03) 99.74	(86.04-101.28) 99.41	-----	-----
CV (%)	15.77	14.18	30.63	-----	-------

*ln-transformed values

Results

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of Monomethyl Fumarate (MMF) of Fumarox 240mg Delayed release Tablet under fast conditions.

Treatment N=43	AUC0-T ng.h/ml	AUC0-∞ ng.h/ml	Cmax ng/ml	tmax h	t1/2 h
Test	3493.32 ± 1174.61 (33.62)	3594.84 ± 1171.24 (32.58)	2148.86 ± 924.75 (43.03)	2.17 (1.17 – 9.00)	0.57 ± 0.11
Reference	3265.60 ± 1051.09 (32.19)	3339.45± 1054.92 (31.59)	1916.95 ± 545.79 (28.47)	3.17 (2.17 - 4.50)	0.59 ± 0.14
*Ratio (90%) CI	(101.06-111.67) 100	(102.14-112.14) 100	(97.39-115.18) 99.08	-----	-----
CV (%)	17.65	17.52	26.39	-----	-------

*ln-transformed values

Conclusion

-The 90% confidence intervals calculated for **$AUC_{0-\infty}$**, AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 80%-125%.

-Based on those studies demonstrated that the Fumarox (Dimethyl Fumarate) 240mg Delayed Release Capsule from ELIXIR PHARMA-Egypt with Tecfidera® (Dimethyl Fumarate) Delayed Release Capsules 240 mg of Biogen Inc. Cambridge are Bioequivalent after a single oral dose of test and reference administration under Fasting & Fed conditions on healthy participants.