EDA Assessment Report for human medicinal product

(Scientific Discussion)

Finlim 0.5 mg Hard Gelatin Capsule

Fingolimod (as Hydrochloride)

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 Finlim 0.5 mg Hard Gelatin Capsule from ELIXIR PHARMA-Egypt.
- The product is indicated for the treatment of multiple sclerosis.

II. Quality Aspect

Drug Substance

- A CEP has been submitted for evaluation.
- The drug substance is white or almost white powder, freely soluble in water and in ethanol (96%), practically insoluble in heptane and exhibits polymorphism (form I).
- The drug substance specifications are Appearance, Solubility, Identification (IR, HPLC & Chlorides), powder X-ray diffraction (PXRD), Water content (KF), Sulphated ash, Chloride content, Related substances (HPLC), Assay (HPLC), Residual solvents (GC), Particle size distribution, Microbiological examination and the content of Methyl Methane Sulfonate (MMS), Ethyl Methane Sulfonate (EMS) and Isopropyl Methane Sulfonate (IPMS) by (GC-MS/MS)
- 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 6 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 under nitrogen in double polyethylene bags (outer black), with silica gel, molecular sieve, and oxygen absorber in between, in triple laminated bags with silica gel, molecular sieve and oxygen absorber placed in a polyethylene drum.
- The retest period of the drug substance is 60 months when preserved in tight, light-resistant containers and stored at 2-8°C.

Medicinal Product

- **Product Description**

-The hard gelatin capsule is size ‘4’ and has bright yellow cap and opaque white body hard imprinted with ‘H’ on cap with black ink and ‘F7’ on body with blue ink, filled with white to off white powder.

-The product is packed in clear PVC/PVdC-Alu blister packs and placed in carton box.

-The excipients used in capsule fill are Powdered Cellulose, Titanium Dioxide and Magnesium stearate.

-The excipients used in capsule shell are Iron oxide yellow (E 172), Titanium dioxide, Gelatin and SLS.

-Composition of black ink: Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Black Iron Oxide and Potassium Hydroxide.

-Composition of blue ink: Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution and FD & C Blue # 2 Aluminum Lake - (Indigo Carmine).

- **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, physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**

-The manufacturing process consists of mixing, lubrication, capsule filling and Packaging.

-The manufacturing process was adequately validated according to relevant guidelines. Validation included validation of specific operating parameters for each step of manufacturing where applicable.

- **Control of excipients**

-All excipients comply with Ph.Eur except for capsule shell which is controlled according to in house specifications.

- **Control of drug product**

-Product specification includes Description, Identification (HPLC & TLC), Average weight of filled capsule, Average net fill content, Lock length, Water content (KF), Uniformity of dosage units (HPLC), Uniformity of mass, Dissolution (HPLC), Related compounds (HPLC), Assay (HPLC), Microbiological examination and Identification of colorants (titanium oxide and Iron Oxide).

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

-Batch Analysis from the proposed production site were provided for 3 commercial batches. 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 “0.025 mm plain aluminum foil (Hard tempered) with 7GSM HSL coating on bright side” and forming film “clear 250 Microns PVC/90 GSM PVdC” placed in carton boxes with package insert.

- **Stability**

-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 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 except gelatin. A declaration of TSE/BSE free is submitted for gelatine used in the manufacture of Finlim hard gelatin capsules.

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 most recent revision of the CEP should be submitted.

For the Drug product:
- A discussion should be provided for the origin of palmitate and stearate amides and other specified impurities whether they are process related impurities from the fingolimod API or degradation products or resulted from the interaction with excipients.

The Quality of the drug product has been found satisfactory after:
-The applicant submitted and updated revision of CEP.
-The applicant provided a detailed description on the origin for various impurities that are likely to be present in the finished drug product.

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

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

Fingolimod is a sphingosine 1-phosphate receptor modulator used to treat patients with the relapsing-remitting form of multiple sclerosis (MS) and studied to manage lung complications of COVID-19.

Fingolimod is indicated for the treatment of patients aged 10 and above with relapsing forms of multiple sclerosis, which may include clinically isolated syndrome, relapsing-remitting disease, as well as active secondary progressive disease.

Mechanism of action:

-Sphingosine-1-phosphate (S1P) is an important phospholipid that binds to various G-protein-coupled receptor subtypes, which can be identified as S1P1–5R. S1P and the receptors it binds to perform regular functions in the immune, cardiovascular, pulmonary, and nervous systems. S1P can be expressed ubiquitously, playing an important role in regulating inflammation. S1P1R, S1P2R, and S1P3R receptors can be found in the cardiovascular, immune, and central nervous systems. S1P4R is found on lymphocytic and hematopoietic cells, while S1P5R expression is found only on the spleen (on natural killer cells) or in the central nervous system.

-The active form of the drug, fingolimod phosphate, is a sphingosine 1-phosphate receptor modulator that exerts its mechanism of action in MS by binding to various sphingosine 1-phosphate receptors (1, 3, 4, and 5). It suppresses the exit of lymphocytes from lymph nodes, leading to a lower level of lymphocytes circulating in the peripheral circulation. This reduces the inflammation that is associated with MS. The mechanism of action of fingolimod is not fully understood but may be related to reduced lymphocyte circulation into the central nervous system.

-Immune modulating treatment such as fingolimod is not typically employed for SARS-CoV-2 pneumonia. Despite this, with the tissue findings of pulmonary edema and hyaline membrane formation, the timely use of immune modulators such as fingolimod can be considered to prevent acute respiratory distress syndrome (ARDS) associated with COVID-19.

Pharmacokinetics

Bioequivalence Study

-The bioequivalence study of Finlim 0.5mg Hard Gelatin Capsule from ELIXIR PHARMA-Egypt was done relative to Gilenya® 0.5 mg hard capsules Novartis Europharm Limited, U.K. administered to healthy participants.

Design

-The Study was an open label, balanced, randomized, two-treatment, single period, Single oral dose, parallel bioequivalence study of Finlim 0.5 mg (0.5 mg x 3 capsules) hard capsule of ELIXIR PHARMA-Egypt with Gilenya® 0.5 mg (0.5 mg x 3 capsules) hard Capsules of Novartis Euro Pharm Limited, UK in normal, healthy, Adult, human subjects under fasting condition.

Analytical Methods

-All procedures used to perform the bio-analyses of Fingolimod 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 Product name and strength under fast

Treatment N=59	AUC0-72 Pg.h/ml	Cmax Pg/ml	tmax h*
Test	83600.803 ± 15421.9065	1464.539 ± 263.1192	16
Reference	78560.023 ± 11706.5617	1408.374 ± 232.8210	13

*Tmax is represented as median (min-max) value.

The relative bioavailability analyses (i.e. geometric least squares mean, ratio, 90% confidence intervals, inter subject CV and power) of Test Product-T vs. Reference Product-R for Fingolimod are summarized in the following table:

Relative Bioavailability Results for Fingolimod (N = 59)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Subject CV (%)	Power (%)
	Test Product-T (N = 29)	Reference Product-R (N = 30)	Ratio T/R(%)			
AUC0-72 Pg.h/ml	82147.703	77753.511	105.7	98.32 - 113.53	16.6	100.0
Cmax Pg/ml	1439.561	1390.756	103.5	95.99 - 111.62	95.99 - 111.62	99.9

Conclusion

-The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25.

-Based on this study demonstrated that Fingolimod in Finlim 0.5 mg Hard Gelatin Capsule from ELIXIR PHARMA-Egypt & Gilenya® 0.5 mg hard capsules from Novartis Europharm Limited, UK. are Bioequivalent after a single oral dose of test and reference administration under Fasting on 59 healthy participants.