Arab Republic of Egypt
Egyptian Drug Authority
CAPP

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الصيدلية

EDA Assessment Report for human medicinal product

(Scientific Discussion)

Apexlimod 0.5mg, Hard Gelatin Capsules

(Fingolimod)

Date: December 2023

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Apexlimod 0.5mg Hard Gelatin Capsules from Apex Pharma.

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

II. Quality Aspect

Drug Substance

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is off- white to white powder. It is freely soluble in water and alcohol. Fingolimod is non-hygroscopic and has no chiral centers, so it doesn't exhibit isomerism however it exhibits polymorphism and the manufacturing process adopted by the supplier produces Form I.
- The synthesis of drug substance consists of five stages, with the formation of two intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, FTIR, UV Spectroscopy, Nuclear Magnetic Resonance (1H and 13C) and the structure is well characterized. Fingolimod shows polymorphism, polymorphic evaluation report (by P-XRD, DSC and TGA) is submitted to prove Form-I polymorph.
- The drug substance specifications include the following tests description, solubility, identification (IR, by melting point), XRPD, water content (by Karl Fischer), residue on ignition, chloride content, particle size, related substances (by HPLC), assay, residual solvents (by GC) and microbial examination. 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.
- Fingolimod Hydrochloride is packed in inner transparent LDPE bag, then inserted in black LDPE bag along with silica gel, then it is inserted in TLMB (Triple Laminated Medium Barrier) bag with silica gel, which is placed in tightly capped HDPE drum.

  Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.

- Stability of API is submitted (accelerated at 25±2°C/60±5% RH) and long term at 5+3°C and conclude the conformity of specifications during the retest period and storage conditions. The storage conditions for Fingolimod are "Preserve in tight, light-resistant containers. Store at 2-8°C".

Medicinal Product

Product Description

- Hard gelatin capsule size 3, with opaque orange cap & opaque orange body containing white to off white powder.
- Carton box containing Alu/Alu blisters each of 10 hard gelatin capsules and inner leaflet.
- The excipients are: Mannitol (pearlitol 100 SD) and Magnesium stearate.
  Capsules includes: Gelatin, Methyl paraben, Propyl Paraben, Sodium lauryl Sulphate, Aerosil, Titanium dioxide, Quinoline Yellow, Erythrosine Red.
- **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 sieving, mixing, dry granulation, milling, final blending and encapsulation.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three commercial batches.
- Control of excipients, all excipients comply with USP and BP except for Quinoline yellow, Erythrosine red are in-house and the specifications of the excipients are acceptable.
- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests uniformity of mass of capsule content, water content, disintegration, dissolution, uniformity of dosage units (content uniformity) and Microbiological examination. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for three production scale batches, demonstrating compliance with the release specification.
- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.

- Stability of Finished Pharmaceutical Product is submitted (accelerated at 40°C ± 2°C/75% RH ± 5% RH) and long-term at 30°C ± 2°C/65% RH ± 5% RH) and conclude the conformity of specifications during the shelf-life and storage conditions. The storage conditions for the finished pharmaceutical product are "store at temperature not exceeding 30°C, in dry place".
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
- A declaration/certificate of TSE/BSE free is submitted.

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:

- To assure the safety of the API the control strategy option for possible formation of isopropyl chloride during synthesis was required to be submitted by the supplier.

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

-The applicant has submitted a clarification from the API supplier the control strategy option for possible formation of isopropyl chloride during synthesis.

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

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

Fingolimod is an orally available derivate of myriocin and sphingosine-1-phosphate receptor 1 (S1PR1, S1P1) modulator, with potential anti-inflammatory and immunomodulating activities. Upon oral administration, fingolimod, as a structural analogue of sphingosine, selectively targets and binds to S1PR1 on lymphocytes and causes transient receptor activation followed by S1PR1 internalization and degradation. This results in the sequestration of lymphocytes in lymph nodes. By preventing egress of lymphocytes, fingolimod reduces both the amount of circulating peripheral lymphocytes and the infiltration of lymphocytes into target tissues. This prevents a lymphocyte-mediated immune response and may reduce inflammation. S1PR1, a G-protein coupled receptor, plays a key role in lymphocyte migration from lymphoid tissues. Fingolimod also shifts macrophages to an anti-inflammatory M2 phenotype, and modulates their proliferation, morphology, and cytokine release via inhibition of the transient receptor potential cation channel, subfamily M, member 7 (TRPM7).

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Apexlimod 0.5 mg Hard gelatin Capsules, (Apex Pharma, Egypt) relative to Gilenya™ 0.5 mg Hard gelatin Capsules on 27 healthy subjects under fasting conditions.

Design

A Comparative, Open-Label, Single Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, Fasting, Crossover Bioequivalence Study with a Washout Period of Seven weeks Between periods in healthy participants.

On randomized manner each subject received single oral dose from test & reference products directly into mouth administrated by 240ml water after overnight fasting (at least 8-10 hours in fasting) according to the randomization sheet.

Blood Sampling: pre-dose blood sample were withdrawn at 0.00, 2.00, 4.00, 6.00, 8.00, 9.00, 10.00, 11.00, 11.50, 12.00, 12.50, 13.00, 13.50 14.00, 14.50, 15.00, 15.50 16.00, 16.50, 17.00, 18.00, 20.00, 22.00, 24.00, 36.00, 48.00 and 72.00 hrs.

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. 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 Fingolimod 0.5 mg under fast condition.

Treatment N=27	**AUC_{0-72} pg.h/ml**	**C_{max} pg/ml**	**T_{max} h**
Test	17132.16 ± 9255.99	413.56 ± 179.93	12.00
Reference	18701.56 ± 9092.77	426.27 ± 201.54	12.50
***Ratio (90%) CI**	90.36% (82.21%-99.32%)	99.68% (92.62%- 107.27%)	-------
CV (%)	-------	-------	-------

*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 Fingolimod in the test product, Apexlimod 0.5 mg Hard Gelatin Capsules & reference product, Gilenya™ 0.5 mg Hard Gelatin Capsules are Bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 27 participants.