EDA Assessment Report for human medicinal product

(Scientific Discussion)

Apixguard 2.5mg & 5mg

(Apixaban)

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 "Apixguard 2.5mg & Apixguard 5mg Film Coated Tablets" from Marcyrl Pharmaceutical Industries.

The product contains the active substance "APIXABAN" which is a factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

II. Quality Aspect

Drug Substance

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- Apixaban is a white to cream colored powder, non-hygroscopic, slightly soluble in methanol and dimethyl sulfoxide, Apixaban exhibits polymorphism and API manufacturer produces form N1 (Anhydrous), which is characterized by powder p-XRD.
- The synthesis of drug substance includes 3 steps with the formation of two intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR, UV, H^1 NMR, C^{13} NMR and DEPT-135, Mass spectroscopy, Elemental analysis, DSC, TGA and XRPD. The structure is well characterized.
- The drug substance specifications are in accordance with in-house test and include the following tests description, solubility, identification by (IR & HPLC), XRPD (specifying the type of the used polymorph), water content, residue on ignition, related substances, assay, residual solvents, acetic acid content by HPLC and particle size distribution. All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of three drug substance batches demonstrating compliance with the current drug substance specification.
- Apixaban is packed in a white LDPE bag twisted and tied, then inserted in a black LDPE bag twisted and tied then placed into a tightly capped HDPE drum with a metallic seal and metallic ring for the drum.
- Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.
- Stability of API have been performed on 3 validation batches for long-term at (25°C/ 60 RH% simulated commercial packaging) and for accelerated stability study at (40°C / 75 RH% - simulated commercial packaging) respectively and conclude the conformity of specifications during the retest period and storage conditions. The recommended storage conditions are "Preserve in tight, light-resistant containers and Store at 25°C, excursions permitted between 15°C and 30°C".

Medicinal Product

- **Product Description:**
  - **For 2.5 mg**: is yellow to dark yellow round biconvex film coated tablet with core consists of white to off white round biconvex tablet and average weight of 103mg
    The product is packed in: carton box containing 1,2 or 3 (Al/transparent PVC/PVDC) strips, each of 10 film coated tablets & inner leaflet.
  - **For 5 mg:** is yellow to dark yellow round biconvex film coated tablet with core consists of white to off-white round biconvex tablet and average weight of 206 mg
    The product is packed in: carton box containing 1,2 or 3 (Al/transparent PVC/PVDC) strips, each of 10 film coated tablets & inner leaflet.
  - The excipients are: Lactose monohydrate 200 Mesh, Microcrystalline Cellulose 101 (Avicel PH101 or Equivalent), Maize starch, Polyvinylpyrrolidone (PVP) K30, Croscarmellose sodium, Magnesium Stearate, Purified water, (for tablet core) and Opadry® II Yellow (Code: 85G32507) which composed of (Polyvinyl Alcohol - Titanium Dioxide - Macrogol/PEG (MW 3350) - Talc - Lecithin - Iron Oxide Yellow - Quinoline Yellow Aluminum Lake – FD&C Yellow #6 / Sunset yellow FCF Aluminum Lake – FD&C Blue #2 / Indigo Carmine Aluminum Lake (for tablet coat).

❖ **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. also, the effect of particle size distribution test on the dissolution of the Tablets was addressed and the acceptance criteria of the Particle size was optimized based on the comparative dissolution study.
Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

❖ Manufacturing process, the manufacturing process consists of mixing, sieving, wet granulation, drying, milling, lubrication, compression & coating.

❖ Control of excipients, all excipients comply with USP except for Opadry® II Yellow follows (in-house) specifications and the specifications of the excipients are justified.

❖ Product specification includes the four universal tests for description, identification (by HPLC PDA), assay, impurities and additional tests: uniformity of mass, loss on drying: disintegration, dissolution test (by HPLC), uniformity of dosage unit by Content Uniformity (by HPLC), Microbiological analysis, all limits are acceptable.

❖ Analytical methods were adequately described and validated.

❖ Batch Analysis from the proposed production site were provided three primary batches of each strength, demonstrating compliance with the release specification.

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

❖ Stability of finished pharmaceutical product is submitted under accelerated conditions at (40°C/75 %RH) and long-term conditions at (30°C°C/ 65%RH) and concluded the conformity of specifications

during the shelf-life and storage conditions. Apixguard 2.5mg & Apixguard 5mg Film Coated Tablets should be stored at a temperature not exceeding 30°C, in dry place.

- ❖ Specific measures concerning the prevention of the transmission of animal spongiform encephalopathy, a declaration/certificate of TSE/BSE free is submitted for substances of animal origin.

Summary basis of opinion:

From Chemistry, Manufacture and Control perspective, the main concern found during the evaluation process was as follow:

For the drug product:

-The applicant was asked to justify the absence of control of acid impurity in the finished pharmaceutical product which is identified by the API supplier as degradation impurity.

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

- The applicant declared that this impurity is controlled under the limit of unspecified impurities in finished product specifications.

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

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

Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions & Treat deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Apixaguard 5 mg Film Coated Tablet, (Marcyrl pharmaceutical industries,) relative to Eliquis ® 5 mg Film Coated Tablet administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Apixaguard 2.5mg film-coated tablets based on the following arguments:

- The qualitative and quantitative composition of the different strengths is dose proportional and only differs in the film coating, which is acceptable and in accordance with the guideline.
- Both strengths of Apixaguard are manufactured by the same process.
- Apixaban has linear pharmacokinetics over the therapeutic dose range.
- Both tablet strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

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

On randomized manner each subject received single oral dose from test & reference products directly into mouth administrated by 240 ml 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, 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 36 and 48 hours after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Apixaban 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 Apixaban 5 mg under fast condition.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	T_{max} h	$t_{1/2}$ h
Test	1579.90009± 496. 211	1618.13970± 513.456	149.49± 45.12	3.50	9.28± 1.97
Reference	1543.28469± 434. 637	1584.60526± 458. 349	155.68± 39.92	3.50	9.41± 2.56
***Ratio (90%) CI**	101.57 (95.38- 108.16)	101.35 (95.24- 107.84)	94.97 (88.65- 101.75)	-------	--------
CV (%)	-------	-------	-------	-------	------

*ln-transformed values
* Vol 15 withdraw after dosing at phase I, at 3.5 hrs time interval.
*Vol 22 withdraw after dosing at phase II, at 2 hrs time interval

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 Apixaban in the test product, Apixaguard 5mg Film Coated Tablet, (Marcyrl pharmaceutical industries) & reference product, Eliquis ® 5mg Film Coated Tablet are Bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 24 participants.