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)

Gabaverona Hard Gelatin Capsules

(Gabapentin 100, 300 & 400mg)

Date: September 2023

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Gabaverona 100mg, 300mg & 400mg from Averroes Pharma for Pharmaceutical Industries.

The product is indicated for:

- Postherpetic neuralgia in adults.
- Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy.

II. Quality Aspect

Drug Substance

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to off white crystalline powder, hygroscopic. It is freely soluble in water, in alkaline and acidic solution. Gabapentin exhibits polymorphism (has four crystalline forms).
- The synthesis of drug substance includes two steps. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, FT-IR, ^{1}H-NMR, ^{13}C-NMR, XRPD and the structure is well characterized.
- The drug substance specifications are in accordance with "USP" specifications and include the following tests: description, identification, water determination, pH, solubility, assay by HPLC, related substances, & residual solvents. All limits are acceptable.
- Analytical methods were adequately described and validated.
- 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 and conclude the conformity of specifications during the shelf-life and storage conditions

Medicinal Product

- **Product Description**

Hard gelatin capsule contains white to off white powder in:

- 100mg strength (green body; green cap).
- 300mg strength (brown body, brown cap).
- 400mg strength (white body, white cap).

- The product is packed in opaque white (PVC/PVDC/ Plain Aluminum) strip, of 10 Hard Gelatin Capsules.
- The excipients are: Lactose spray dried, Maize starch and Talc.

Capsules include: Gelatin, methyl paraben, propyl paraben, sodium lauryl sulfate, Aerosil 200, Titanium dioxide and colorants.

- **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 consists of dry mixing and capsule filling.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three primary size batches.
- Control of excipients, all excipients comply with USP/BP Pharmacopeia and the specifications of the excipients are justified.
- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests: uniformity of mass of capsule content, uniformity of mass of total capsule, average weight of capsule shell, uniformity of dosage unit, disintegration test, dissolution test & microbiological tests. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided 3 primary batches of each strength, 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 and conclude the conformity of specifications during the shelf life and storage conditions.
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, a declaration of TSE/BSE free is submitted for substances of animal origin.

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

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

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

Gabapentin is indicated for:

1- Epilepsy: as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above.

2- Treatment of peripheral neuropathic pain: is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Gabaverona 400mg Hard Gelatin Capsules (Manufactured by: Averroes Pharma for Pharmaceutical Industries, Egypt) relative to the reference product Neurontin ® 400mg Capsules (Manufactured by Pfizer, France) administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strengths Gabaverona 100 & 300mg Hard Gelatin Capsules on the basis of bioequivalence study conducted on Gabaverona 400mg based on the following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- Both strengths of Gabaverona are manufactured by the same process.
- Gabaverona 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-Sequence, Two-Period, crossover bioequivalence study under fasting conditions with a washout period of one week between each study period in healthy participants.

On randomized manner each subject received one tablet from test or one tablet from reference directly into mouth administrated by 240 ml water after overnight fasting (at least 8-10 hours in fasting).
Blood sampling schedule: (Pre-dose, 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36 Hours).

Analytical Methods

All procedures used to perform the bio-analyses of Gabapentin 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 Gabaverona 400mg Hard Gelatin Capsules (Gabapentin 400mg) under fasting conditions.

Treatment N=26	C_{max} µg/ml	T_{max} (hr)	AUC_{0-t} (µg.hr/ml)	AUC_{0-inf} (µg.hr/ml)	$t_{1/2}$ (hr)
Test	3.49± 0.84	3.98	37.23777 ± 9 .836	39.79852 ± 11.672	6.42± 1.76
Reference	3.35± 1.27	3.5	34.90495± 12.778	38.02346 ± 15.834	7.14± 1.47
***Ratio (90%) CI**	107.59 (96.78-119.61)	-------	109.87 (100.4-120.24)	108.39 (96.67-121.54)	-------

*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 the Active Pharmaceutical Ingredient of Gabapentin in Hard Gelatin Capsules of The Test Product, Gabaverona 400mg Hard Gelatin Capsules (Manufactured by: Averroes Pharma for Pharmaceutical Industries, Egypt) & reference product, product Neurontin ® 400mg Capsule (Manufactured by Pfizer, France) are bioequivalent after a single an oral dose of test and reference administration under fasting conditions on 26 participants.