# EDA Assessment Report for human medicinal product

(**Scientific Discussion**)

## Sherogastric 20mg & 40mg

## Film Coated Tablets

## ( Famotidine)

**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 Sherogastric 20mg & 40mg film coated tablets (Famotidine) from Averroes Pharma for Pharmaceutical Industries.

The product is indicated for:

- Symptomatic relief of heartburn, dyspepsia and indigestion due to gastro-oesophageal reflux in adults over 18 years of age.
- For the treatment of duodenal ulcer; benign gastric ulcer; Zollinger-Ellison syndrome; prevention of relapses of duodenal ulceration.
- Short-term (no more than 12 weeks) symptomatic relief of gastro-oesophageal reflux not responsive to conservative measures.
- Healing of oesophageal erosion or ulceration associated with gastro-oesophageal reflux disease.
- Prevention of relapses of symptoms and erosions or ulcerations associated with gastro-oesophageal reflux disease.

# II. Quality Aspect

**Drug Substance**

- APIMF (applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to pale yellowish-white crystalline powder, freely soluble in dimethyl formamide and in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, practically insoluble in acetone, ether, alcohol, chloroform and in ethyl acetate, Famotidine has no chiral center, and the supplier produced Form-B polymorph.
- The synthesis of drug substance includes four steps with the formation of three intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR and UV spectroscopy, $^{1}H$ NMR, $^{13}C$ NMR, mass spectroscopy, elemental analysis, XRD and DSC, the structure is well characterized.
- The drug substance specifications are in accordance with USP and include the following tests: description, solubility, identification by IR, loss on drying, residue on ignition, organic impurities, assay and 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**

- White to off white round biconvex tablets, plain from one side plus sign contain A, V, S and P symbols from the other side.
- The product is packed in cartoon box containing a strip of 10 tablets of "Aluminum foil/white opaque triplex (PVC /PE/PVDC)".
- The excipients are: pregelatinized starch, microcrystalline cellulose, colloidal silicon dioxide, talc & magnesium stearate (for tablet core) and Hypromellose, polyethylene glycol, talc & titanium dioxide (for coating).
- 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 mixing, direct compression and coating.
- The manufacturing process was adequately validated according to relevant guidelines for three primary batches.
- Control of excipients, all excipients comply with USP, 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, disintegration time, dissolution, uniformity of dosage units by content uniformity and microbial tests, all limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch analysis from the proposed production site were provided for three 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.
- There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

**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**

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

Famotidine is a competitive histamine-2 (H2) receptor antagonist that works to inhibit gastric acid secretion. It is commonly used in gastrointestinal conditions related to acid secretion, such as gastric ulcers and gastroesophageal reflux disease (GERD), in adults and children. Compared to other H2 receptor antagonists, famotidine displays high selectivity towards this receptor.

Famotidine is indicated for:

- Duodenal ulcers and prevention of relapses of duodenal ulceration.
- Benign gastric ulcers.
- Zollinger-Ellison syndrome.
- Symptomatic treatment of mild to moderate reflux oesophagitis.

**Pharmacokinetics**

**Bioequivalence Study**

The bioequivalence study of test product Sherogastric 40mg film coated tablet (produced by Averroes Pharma for Pharmaceutical Industries) versus reference product Famotidine USP 40mg tablets produced by Aurobindo Parma Limited, India and distributed by Aurobindo Pharma USA, Inc.) administered to healthy participants.

**Biowaiver**

The EDA was granted a biowaiver for the lower strength Sherogastric 20mg film coated tablet 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 Sherogastric are manufactured by the same process.
- Entecavir 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 Oral Dose, Randomized, Two-Period, Two-Treatment, Two-Sequence, Two-Way Crossover Bioequivalence Study with a Washout Period of Seven Days between periods in healthy participants under Fasting condition.

Subjects of at least 18 years of age but not older than 55 years with a body mass index (BMI) greater than or equal to 18.5 and less than or equal to 30 kg/m2 were included in the study. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and clinical laboratory tests (biochemistry, hematology, lipid profile, urinalysis) including negative virology for HIV, Hepatitis B and Hepatitis C tests as well as negative screening of drugs of abuse in urine.

At each phase, the subjects received one film coated tablet containing 40 mg Famotidine from either Sherogastric (test product) or Famotidine USP (reference product) with 240 mL of water at room temperature following an overnight fast of 10 hours in accordance with the randomization plan.

Blood samples were collected prior to dosing (Pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 12, and 24 hours after drug administration.

## Analytical Methods

All procedures used to perform the bio-analyses of Famotidine 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

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t max (median, range) of Sherogastric 40mg film coated tablet under Fasting condition.

| Treatment N=30 | $AUC_{0-t}$ ng.h/ml | $AUC_{0-inf}$ ng.h/ml | $C_{max}$ ng/ml | $T_{max}$ ( hr) | $t_{1/2}$ (hr) | $k_{el}$ (hr) |
|---|---|---|---|---|---|---|
| **Test** | 468.080± 128.964 | 484.274± 133.490 | 60.095 ±16.100 | 2.250 | 4.678± 0.631 | 0.151 |
| **Reference** | 446.232± 142.345 | 462.787± 148.656 | 58.905± 20.650 | 1.875 | 4.620± 0.620 | 0.153 |
| ***Ratio (90%) CI** | 105.30383 (97.55675 - 113.66612) | 105.09274 (97.46341 - 113.31929) | 103.16978 (94.98889 - 112.05524) | --------- | --------- | --------- |
| **CV (%)** | 17.49% | 17.25% | 18.93% | --------- | --------- | --------- |

*ln-transformed values

*Thirty-two (32) subjects were enrolled& participated in the study, thirty (30) subjects who completed all study periods and cross over included in pharmacokinetics and statistical analysis,
as subject#11 was excluded after dosing of period I due to selection criteria, while subject#20, withdrew for personal reasons before admission to the clinical site for phase II.

**Conclusion**

The 90% confidence intervals calculated for $C_{max}$, AUC $_{0-t}$ and AUC $_{0-inf}$ are within the bioequivalence acceptance range of 80 – 125%.

Based on this study demonstrated that the active pharmaceutical ingredient of Famotidine in the Test Product Sherogastric 40mg film coated tablet (produced by Averroes Pharma for Pharmaceutical Industries) versus reference product Famotidine USP 40 mg tablets (produced by Aurobindo Parma Limited, India and distributed by Aurobindo Pharma USA, Inc.) are Bioequivalent after a single an oral dose of test and reference administration under Fasting conditions on 30 participants.