EDA Assessment Report for human medicinal product

(Scientific Discussion)

Esmosalix 40 mg Hard Gelatin Capsules containing enteric coated pellets

(Esomeprazole as Magnesium Trihydrate)

Date: October 2023

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Esmosalix 40 mg hard gelatin capsules containing enteric coated pellets from Salix Pharma.
- The product contains the active substance "Esomeprazole" which suppresses gastric acid secretion by specific inhibition of H+/K+-ATPase in the gastric parietal cell. It belongs to a group of medicines called "Proton Pump Inhibitors" PPIs. It is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is substance white or slightly colored powder which is slightly soluble in water, soluble in methanol, practically insoluble in heptane. It is sparingly soluble in ethanol, acetic acid, chloroform, very slightly soluble in isopropyl alcohol and practically insoluble or insoluble in dichloromethane, toluene, benzene and acetone. It is slightly hygroscopic in nature and it is optically active isomer **(S-isomer)**. It exhibits polymorphism **(Form I)**.
- The synthesis of drug substance includes two steps to produce Esomeprazole magnesium trihydrate through the formation of one isolated intermediate. The two starting materials, all reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, FTIR, UV Spectroscopy, Nuclear Magnetic Resonance (^{1}H and ^{13}C) and the structure is well characterized. The polymorphism **Form-I** is confirmed via P-XRD, DSC and TGA. The S-isomer is controlled via chiral HPLC technique.
- The drug substance specifications are in accordance with "European pharmacopeia" specifications and include the following tests: description, solubility, identification (IR and enantiomeric purity), water content (Karl Fischer), enantiomeric purity (HPLC), assay (HPLC), related substances (HPLC), magnesium content (titrimetric determination) and microbiological tests. In-house specifications were added including residual solvents (GC), acetic acid content (HPLC) and cumene related impurities (HPLC). all limits are acceptable.
- All analytical procedures were adequately described and well validated.
- The applicant provided batch analysis results of 6 drug substance batches demonstrating compliance with the current drug substance specification.

- The API is packed in double lined low-density food grade polyethylene bags (transparent inner and black outer) tie with plastic fastener (Primary packing) followed by HDPE drum (Secondary packing). 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 40°C±2°C / 75±5%RH and long term at 25°C±2°C / 60±5%RH) and conclude the conformity of specifications during the retest period and storage conditions. The storage conditions for Esomeprazole magnesium trihydrate are "Store in airtight containers, protected from light. at 25°C".

Medicinal Product

Product Description

- Esmosalix Hard Gelatin Capsules are available as Violet Cap & Violet body containing enteric coated White to off white pellets.
- The product is packed in ALU/ PVC strip containing 7 H.G.C in a printed color carton box containing 1 or 2 or 3 strip(s).
- The excipients for the **pellets** are: sugar spheres (25#30) used as a core material, mannitol, hypromellose, polysorbate 80 and sodium hydroxide are used for drug loading stage. Hypromellose, polyethylene glycol 6000, talc and titanium dioxide are used for barrier coating stage. Hypromellose phthalate, cetyl alcohol, talc and titanium dioxide are used for enteric coating stage.
- **Both Cap violet and Body violet** consist of: gelatin, methyl paraben, propyl paraben, sodium lauryl sulfate, silica colloidal anhydrous (Aerosil 200), titanium dioxide, erythrosine red, brilliant blue.

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 of the enteric coated pellets includes 3 stages (Drug Layering, Barrier Coating & Enteric Coating), manufacturing process of Hard Gelatin Capsules is done by Capsule filling, Blistering and Final packaging.
- The manufacturing process of enteric coated pellets was adequately validated by the manufacturer of enteric coated pellets and includes 3 commercial batches.
- The manufacturer process of Hard Gelatin capsules was adequately validated by FPP manufacturer according to relevant guidelines. Validation included three primary sized batches.

Control of excipients

- All excipients used in capsule body and cap comply with British pharmacopeia except for gelatin and titanium dioxide which comply with USP. While, erythrosine red, brilliant blue "coloring agents" are In-house. The specifications of the excipients are well justified.

Product specification

- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests including mass uniformity, uniformity of dosage unit (by content uniformity), dissolution, disintegration & microbiological tests. All limits are acceptable.
- Analytical methods were adequately described and well validated.
- Batch Analysis from the proposed production site were provided 3 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 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".
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, a declaration/certificate 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

Esomeprazole is well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
Esomeprazole is indicated for the treatment of Gastro-Esophageal Reflux Disease (GERD) & used in combination with antibacterial for eradication of Helicobacter pylori.
Esomeprazole inhibits the enzyme H+K+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Esomesalix 40mg hard gelatin capsules containing enteric coated pellets (Esomeprazole 40mg) Licensed by: Salix Pharma relative to the reference product Nexium 40mg Delayed Release Capsuled (Esomeprazole 40mg) produced by: AstraZeneca Pharmaceuticals LP Wilmington administered to healthy participants.

Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Two-Sequence, Four Period, crossover bioequivalence study with a washout period of one week between periods under fasting conditions 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, 0,10 min, 20 min, 30 min, 40 min, 50 min, 1, 1:15, 1:30, 1:45, 2, 2:15, 2:30, 2:45, 3, 3:30, 4, 5, 6, 7, 8, 10 & 12 hour after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Esomeprazole 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 **Esomesalix 40mg** under fast conditions.

Treatment N=28	AUC0-t (ng.h/ml)	AUC0-inf (ng.h/ml)	Cmax (ng/ml)	tmax (h)	$T_{1/2}$ (h)
Test	1527.55	1549.57	585.04	2.8	1.32
Reference	1483.32	1507.42	592.90	2.6	1.32
***Ratio (90%) CI**	105.07 (98.53-112.06)	104.90 (98.39-111.85)	100.54 (90.34-111.88)	------	-----

*ln-transformed values

Conclusion

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

Based on this study demonstrated that Esomesalix 40mg of the test product Esomesalix 40mg hard gelatin capsules containing enteric coated pellets (Esomeprazole 40mg) Licensed by: Salix Pharma relative to the reference product Nexium 40mg Delayed Release Capsuled (Esomeprazole 40mg) Produced by: AstraZeneca Pharmaceuticals LP Wilmington are bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 28 participants.