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)

Pantopram 40mg Delayed Release Tablets

Pantoprazole (as sodium sesquihydrate)

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 Mash for Pharmaceutical Industries and Cosmetic (Mash Premiere).

The product is indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

II. Quality Aspect

Drug Substance

- APIMF (applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to off white powder. Pantoprazole is freely soluble in water, in methanol and in dehydrated alcohol, practically insoluble in hexane and in dichloromethane.
- 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 spectroscopy, proton nuclear magnetic resonance spectroscopy (^{1}H NMR), carbon nuclear magnetic resonance spectroscopy (^{13}C NMR), fluoro nuclear magnetic resonance spectroscopy (^{19}F-NMR), Elemental analysis, Mass Spectroscopy and UV Spectroscopy. The structure is confirmed and well characterized.
- The drug substance specifications are in accordance with USP and include the following tests description, solubility, identification, water content, organic impurities, assay, residual solvents, bulk density, microbial limits and bacterial endotoxins. 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**
- Pale to deep yellow, round, biconvex non-scored delayed release tablets.
- The product is packed in a carton box contains 1, 2 or 3 (Hard Aluminum/ Soft Aluminum (PA/AL/PVC)) strip of 7 delayed release tablets with inner leaflet.
- The excipients are: Mannitol, Crospovidone, Sodium Carbonate Anhydrous, Povidone K30, Calcium Stearate (present in tablet core). Hypromellose, Macrogol, Titanium dioxide, Talc, Eudragit, Dibutyl phthalate, Purified Talc & Ferric oxide yellow (present in film-coating, including enteric coating and sub 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.
- 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, wet granulation, lubrication, compression, coating and packaging.
- The manufacturing process was adequately validated according to relevant guidelines. The company committed to provide validation for the first three production batches.
- Control of excipients, all excipients comply with USP or BP except for Dibutyl phthalate and the specifications of the excipients are justified.
- Product specification includes the four universal tests (description, identification, assay & impurities) and additional tests of uniformity of mass, disintegration, dissolution, residual solvents and microbial limits. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for 3 primary batches, demonstrating compliance with the release specification.
- Container closure system is suitable to store the finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.
- Stability of the 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, 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

Pantoprazole is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. Pantoprazole which blocks the 'pump' that produces stomach acid. Hence it reduces the amount of acid in your stomach. It is indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

Pharmacokinetics
Bioequivalence Study

The Bioequivalence Study of Test Product Pantopram 40mg Delayed Release Tablet (Manufacturer & License Holder: Mash for Pharmaceutical Industries and Cosmetic (Mash Premiere)) Versus Reference Product Controloc ® 40mg Gastro Resistant Tablet (Manufactured By: Takeda GmbH Production Site - Germany) Administered to Healthy Participants.

Design
A Comparative, Open-Label, single oral dose, randomized, Two-way Two-period, Two-treatment, Two-sequence, Un-replicated Crossover Bioequivalence Study with a washout period of seven days between periods in healthy participants under Fasting condition.

Subjects were healthy, adults, aged eighteen to fifty years (18 - 55) within the accepted limits for and meeting the selection criteria for this study.

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, 0.25, 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, 6, 8, 10, 12 & 24 hours post dose.

Analytical Methods
All procedures used to perform the bio-analyses of Pantoprazole 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 Pantopram 40mg Delayed Release Tablet under Fasting condition.

Treatment N=29	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	7101.36± 7442.85	7934.82± 8734.53	2614.87 ± 818.73	2.5	1.81± 2.1	0.67853
Reference	7454.18± 8148.25	9252.64± 10017.4	2627.29 ±1090.07	2.75	1.96± 2.45	0.69347
***Ratio (90%) CI**	97.57 (85.15-111.81)	95.01 (84.18-107.24)	102.23 (85.47-122.27)	---------	---------	---------
CV (%)	--------	---------	31.31	---------	---------	---------

*ln-transformed values

* Thirty (30) subjects were enrolled& participated in the study, Twenty - nine (29) subjects who completed all study periods and cross over included in pharmacokinetics and statistical analysis,
as Vol. (29) withdrawn at 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 0.80 – 1.25.

Based on this study demonstrated that the active pharmaceutical ingredient of Pantoprazole in Delayed Release Tablet of the Test Product Pantopram 40mg Delayed Release Tablet (Manufacturer & License Holder: Mash for Pharmaceutical Industries and Cosmetic (Mash Premiere)) versus Reference Product Controloc ® 40mg Gastro Resistant Tablet (Manufactured by: Takeda GmbH Production site – Germany) are Bioequivalent after a single an oral dose of test and reference administration under Fasting conditions on 29 participants.