EDA Assessment Report for human medicinal product

(Scientific Discussion)

Gastropexy 10 & 20 mg film coated tablet

Vonoprazan (as Fumarate)

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 Gastropexy Film Coated Tablets from Apex Pharma.

The product is indicated for:

1-Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration.

2– Adjunct therapy to Helicobacter pylori eradication in the following: Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or Helicobacter pylori gastritis.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white to an off-white to white crystalline powder. Vonoprazan is slightly soluble in dimethyl sulfoxide, methanol and in water. Vonoprazan exhibits polymorphism.
- The synthesis of drug substance includes 2 manufacturing process steps with the formation of one intermediate (s). All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Infrared Absorption spectrophotometry, Ultra-violet spectrophotometry, Nuclear Magnetic Resonance (^{1}H, ^{13}C), Mass spectrometry and the structure is well characterized. Elemental analysis and identification of polymorphic form were required. The supplier responded by submitting results of elemental analysis and identification of the polymorphic form by XRPD.
- The drug substance specifications are in-house and include the following tests: description, solubility, identification (IR, HPLC), water content, residue on ignition, heavy metals, fumaric acid content, related substances (HPLC), assay (HPLC) and residual solvents (GC). All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of of 3 drug substance batch(es) demonstrating compliance with the current drug substance specification.
- Vonoprazan Fumarate is packed in transparent polythene bag and sealed then kept in black polythene bag and sealed and finally kept in HDPE containers.

- Stability of API is submitted in accelerated storage conditions at (40°C±2°C / 75±5 %RH) and long-term storage conditions at (30°C±2°C/ 75±5%RH) and conclude the conformity of specifications during the shelf-life and storage conditions.
- The results of forced degradation study supported with chromatograms has been required from the supplier. The supplier submitted detailed report of forced degradation study of vonoprazan using different stress conditions and significant change in the content of vonoprazan has been observed when stressed using basic hydrolysis.

Medicinal Product

- **Product Description**
- **10 mg Tablets:** Faint yellow to yellow, round, biconvex, non-scored, film coated tablet, plain from the two sides.
- **20 mg Tablets:** Faint pink to pink, oval, biconvex, scored film coated tablet engraved MAP from one side and scored line from the other side
- The product is packed in Aluminum/Transparent PVC-PVDC blisters placed in carton box.
- The excipients are: Mannitol, Microcrystalline cellulose PH 102, Croscarmellose sodium, Hydroxypropryl cellulose EF, Fumaric acid, Magnesium stearate, Hydroxylpropyl Methylcellulose 2910 E5, Polyethylene Glycol 6000, Talc Purified, Titanium dioxide and colouring agents.
- **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. The applicant was asked to submit the results of comparative in vitro dissolution in different pH dissolution media and the results of similarity factors were found satisfactory.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.
- Manufacturing process, the manufacturing process consists of Sieving & mixing, Granulation, Drying & milling, Final blending and lubrication, Compression & Coating. The drug substance is reported to be photolabile and the precautions taken during the manufacturing process to prevent its degradation has been clarified by the manufacturer.
- The manufacturing process was adequately validated according to relevant guidelines.
- Control of excipients, all excipients comply with all excipients comply with USP/BP and the specifications of the excipients are acceptable.
- Product specification includes four universal tests for description, identification, assay, impurities and additional tests of uniformity of dosage units by content uniformity, uniformity of mass, disintegration, water content and microbial limits. A justification of the high limit of water content has been required

and the applicant responded by modifying the limit (based on trend analysis results of stability study). Based on the provided dissolution profile data, it has been recommended to tighten the limit for dissolution test. The applicant agreed to the administration's recommendation concerning the specification limit of dissolution test and the specifications of the FPP has been revised to include the updated limit.

- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for three 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 in accelerated storage conditions at (40°C±2°C / 75±5 %RH) and long-term storage conditions at (30°C±2°C/ 65±5%RH) and concluded the conformity of specifications during the shelf-life and storage conditions. Gastropexy Film Coated Tablets should be stored at a temperature not exceeding 30°C in dry place.
- 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.

Summary basis of opinion:

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

For the drug substance:

-The limit of specified impurities exceeded the qualification threshold of ICH Q3A guideline therefore a justification has been required.

-Risk assessment of genotoxic impurities for the key starting materials, reagents and intermediates according to ICH M7 has been required.

For the drug product:

-Risk assessment of elemental impurities in the finished pharmaceutical product according to ICH Q3D has been required.

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

-The supplier has revised the limit for the specified impurities to comply with ICH Q3A guideline.

-The supplier has submitted the risk assessment of genotoxic impurities according to ICH M7 and clarified the control strategy to prevent the carry over of potential mutagenic impurities to the final drug substance.

-The applicant has submitted the risk assessment of elemental impurities according to ICH Q3D and the elements that should be considered for oral route of administration were found below their control thresholds.

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

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

Vonoprazan fumarate is indicated for

1-Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration.

2– Adjunct therapy to Helicobacter pylori eradication in the following: Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage gastric cancer, or Helicobacter pylori gastritis.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Gastropexy 20 mg Film Coated Tablets (Apex pharma, Egypt) relative to Takecab 20 mg Film Coated Tablets administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Gastropexy 10 mg Film Coated Tablets (Apex pharma, Egypt) based on the following arguments; both tablet strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

This study was an open label, randomized, fasting, single oral dose, two treatments, two sequences and two periods, crossover study with a washout interval of one week between dosing in healthy participants.

Biological Samples Collection;
Before 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, 3.5, 4, 6, 7, 8, 10, 12, & 14, 24, 36 hours post dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Vonoprazan fumarate 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 Vonoprazan fumarate under fasting conditions.

Treatment N=28	AUC_{0-72} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	161.42 ± 66.87	172.17 ± 73.57	16.56 ± 5.71	2.00	7.43 ± 1.80
Reference	163.33 ± 62.88	172.42 ± 65.98	17.38 ± 5.61	2.00	7.43 ± 1.94
***Ratio (90%) CI**	97.48 (92.15- 103.12)	98.14 (93.42- 103.10)	93.70% (86.73- 101.23)		
CV (%)	---	-------	------		

*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 Vonoprazan fumarate in Gastropexy 20 mg Film Coated Tablets (Apex pharma, Egypt) & Takecab 20 mg Film Coated Tablets are Bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 28 participants.