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)

## Atecazen 0.5 mg & 1 mg film coated tablets

## (Entecavir Monohydrate)

**Date: August 2023**

# I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Atecazen 0.5 mg & 1 mg film-coated tablets from EIPICO.

The product is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with:

- compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis
- decompensated liver disease

# II. Quality Aspect

**Drug Substance**

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white powder, sparingly soluble in dimethylformamide, slightly soluble in methanol, very slightly soluble in ethanol and water, practically insoluble in acetonitrile and heptane. It exhibits polymorphism and there are three chiral centers presented in the molecule.
- The synthesis of drug substance includes five steps with the formation of four intermediate (s). All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via elemental analysis, UV, IR, $H^{1}$NMR, $C^{13}$NMR, Mass and XRPD and the structure is well characterized.
- The drug substance specifications are in accordance with USP and include the following tests description, solubility, identification by IR & HPLC, specific optical rotation, water content by Karl Fischer, related substances, residual solvents, assay and microbiological test. All acceptance criteria are acceptable.
- Analytical methods were adequately described and validated.
- Container closure system is suitable to store the drug substance and comply with food grade packaging material and the specifications are acceptable.
- Stability of the drug substance is submitted and indicate the conformity of specifications during the shelf life and storage conditions.

**Medicinal Product**

- **Product Description**
  - For both concentrations, white to off-white round biconvex Film Coated Tablets with White to off-white round core.
  - The product is packed in carton box containing Alu/Alu cold form strips (tri-laminate foil which consists of Oriented Polyamide, Aluminum Foil & PVC Film) with aluminum foil, each of 10 film coated Tablets.

- The excipients are Lactose Monohydrate DC, Microcrystalline Cellulose PH 102, Povidone K30, Crospovidone (Type A), Magnesium Stearate and Opadry II White (89F18626).
- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions are well explained. It was aimed to develop a product equivalent to the reference product.
  Overall, the choices of the packaging, manufacturing process, overage, physicochemical properties and microbiological attributes are justified.
- Manufacturing process, the manufacturing process consists of bulk preparation, active addition, granulation, sieving, drying, mixing, lubrication and compression.
- The manufacturing process was adequately validated according to relevant guidelines for three primary sized batches for each strength.
- Control of excipients, all excipients comply with BP except for Opadry II White (89F18626) and the specifications of the excipients are acceptable.
- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests including uniformity of mass, loss on drying, disintegration, dissolution, content uniformity and microbiological testing. All acceptance criteria are acceptable.
- Analytical methods were adequately described and validated.
- Batch analysis from the proposed production site was provided for 3 primary batches of each strength, 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 indicate 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/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**

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

Entecavir is indicated for the treatment of chronic hepatitis B virus infection in adults and pediatric patients two years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

**Pharmacokinetics**

**Bioequivalence Study**

The bioequivalence study of Test Product Atecazen 1mg Film Coated Tablet (Manufacturer & License Holder: EIPICO) relative to Reference Product Baraclude® 1mg Film Coated Tablet (Manufactured by Bristol-Myers Squibb Pharma EEIG, Ireland) administered to healthy participants.

**Biowaiver**

The EDA was granted a biowaiver for the lower strength Atecazen 0.5mg film-coated tablets 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 Atecazen 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 Dose, Randomized, Two-Treatment, Two-Period, Two-Sequence, Fasting, Crossover Bioequivalence Study with a Washout Period of Six Weeks Between periods in healthy participants.

**Analytical Methods**

All procedures used to perform the bio-analyses of Entecavir 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 Atecazen 1mg Film Coated Tablet under fasting conditions.

| Treatment N=28 | $AUC_{0-72}$ ng.h/ml | $C_{max}$ ng/ml | $T_{max}$ ( hr) | $t_{1/2}$ (hr) |
|---|---|---|---|---|
| **Test** | 19.267 | 8.315 | 0.830 (0.500-1.750) | 25.617 (3.827-140.180) |
| **Reference** | 18.858 | 7.787 | 0.830 (0.500-2.500) | 27.141 (3.697-93.328) |
| ***Ratio (90%) CI** | 102.43 (96.48-108.75) | 108.32 (98.03-119.68) | --------- | --------- |
| **CV (%)** | 13.155 | 22.091 | --------- | ---------- |

*ln-transformed values

## Conclusion

The 90% confidence intervals calculated for $AUC_{0-t}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25.

Based on this study demonstrated that the Active Pharmaceutical Ingredient of Entecavir 1mg in Film Coated Tablet of the test product, Atecazen 1mg Entecavir Film Coated Tablet (EIPICO) & reference product, Baraclude® (Bristol-Myers Squibb Pharma EEIG) Manufactured by: (Bristol-Myers Squibb Pharma EEIG, Ireland) are Bioequivalent after a single an oral dose of test and reference administration under Fasting conditions on 28 participants.