EDA Assessment Report for human medicinal product

(Scientific Discussion)

Blokatens HCT Film Coated Tablet

Amlodipine 5 mg (as Besylate) + Hydrochlorothiazide 12.5 mg + Valsartan 160 mg
Amlodipine 10 mg (as Besylate) + Hydrochlorothiazide 25 mg + Valsartan 160 mg
Amlodipine 5 mg (as Besylate) + Hydrochlorothiazide 25 mg + Valsartan 160 mg
Amlodipine 10 mg (as Besylate) + Hydrochlorothiazide 12.5 mg + Valsartan 160 mg

Date: May, 2025

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Blokatens HCT Film Coated Tablet from Utopia Pharmaceuticals.
- The product is indicated for the treatment of essential hypertension.

II. Quality Aspect

Drug Substance (Amlodipine Besylate)

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white powder, freely soluble in Methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol and in water. Amlodipine Besylate exhibits Polymorphism. The polymorphic form resulting from the manufacturing process is the crystalline non-hydrate form.
- The synthesis of drug substance includes three steps with the formation of one intermediate.
- The drug substance is elucidated via IR Spectroscopy, UV Spectroscopy, Proton Nuclear magnetic resonance Spectroscopy (^{1}H NMR), Carbon Nuclear magnetic resonance Spectroscopy (^{13}C NMR), Mass Spectroscopy, Powder X-ray Diffraction (P-XRD).
- The drug substance specifications are Description, Solubility, Identification (IR & HPLC), Optical Rotation, Water Content (Karl Fisher), Residue on Ignition, Heavy Metals Content, Related substances (HPLC & TLC), Assay (HPLC) and Residual Solvent (GC).
- Analytical methods are in line with the current version of the USP monograph and are adequately described and validated according to ICH Q2 (R2) guideline.
- The applicant provided batch analysis results of 3 batches. The results of all tests were well within specification limits and batch data was found acceptable.
- The API is packed in transparent polyethylene bags tied with plastic tag, placed in black bag then further placed in HDPE drum.
- Stability of API is submitted in (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 25°C ± 2°C, RH 60% ±5%), and conclude the conformity of specifications during the retest period of 60 months when stored in the proposed container closure system.

Drug Substance (Hydrochlorothiazide)

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white crystalline powder, very slightly soluble in water, freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide, sparingly soluble in methanol, insoluble in ether, in chloroform, and in dilute mineral acids.

- The synthesis of drug substance includes one step with no formation of intermediates.
- The drug substance is elucidated via Elemental analysis, IR Spectroscopy, UV Spectroscopy, Nuclear magnetic resonance Spectroscopy (NMR), Mass Spectroscopy, Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA) and Powder X-ray Diffraction (P-XRD)
- The drug substance specifications are Appearance, Solubility, Identification (IR & UV), Loss on Drying, Residue on Ignition, Chloride content, Selenium content, Heavy Metals Content, Related substances (HPLC), Assay (on the dried basis) (HPLC), Formaldehyde content and Residual solvents (GC).
- Analytical methods are in line with the current version of the USP monograph and are adequately described and validated according to ICH Q2 (R2) guideline.
- The applicant provided batch analysis results of 3 batches. The results of all tests were well within specification limits and batch data was found acceptable.
- The API is packed in low density polyethylene bags then placed in a fibre drum.
- Stability of API is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 30°C ± 2°C, RH 75% ±5%), and conclude the conformity of specifications during the retest period of 36 months when stored in the proposed container closure system.

Drug Substance (Valsartan)

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or off-white powder, freely soluble in Methanol, Ethanol, slightly soluble in dichloromethane, soluble in Acetonitrile, sparingly soluble in ethyl acetate and Practically insoluble in water.
- The synthesis of drug substance includes six steps with the formation of two intermediates.
- The drug substance is elucidated via IR Spectroscopy, UV Spectroscopy, Proton Nuclear magnetic resonance Spectroscopy (^{1}H NMR), Carbon Nuclear magnetic resonance Spectroscopy (^{13}C NMR), Mass Spectroscopy, Elemental analysis, Powder X-ray Diffraction (P-XRD) and Differential Scanning Calorimetry (DSC).
- The drug substance specifications are Appearance, Solubility, Identification (IR & HPLC), Absorbance, Water Content, Residue on Ignition, Related substance (HPLC), Residual solvents (HS-GC), Assay (HPLC) and Particle size distribution.
- Analytical methods are in line with the current version of the USP monograph and are adequately described and validated according to ICH Q2 (R2) guideline.
- The applicant provided batch analysis results of 6 batches. The results of all tests were well within specification limits and batch data was found acceptable.

- The API is packed in polyethylene bag, sealed using a polyethylene tie, packaged in aluminium film bag again, sealed with heat and placed in a fibrous drum.
- Stability of API is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 25°C ± 2°C, RH 60% ±5%), and conclude the conformity of specifications during the retest period of 60 months when stored in the proposed container closure system.

Medicinal Product

- **Product Description**

-Oblong, biconvex, film coated tablet engraved "UTOPIA" from both sides

  - For Blokatens HCT 5/25/160 mg FC Tablets: Beige to yellow
  - For Blokatens HCT 10/12.5/160 mg FC Tablets: Pink to Red
  - For Blokatens HCT 5/12.5/160 mg FC Tablets: Pale yellow to yellow
  - For Blokatens HCT 10/25/160 mg FC Tablets: Faint red to dark red

-The product is packed in Carton box containing 1 or 2 blisters (lidding Alu. foil/CF foil (PVC-AL-OPA), each of 14 film coated tablets engraved "UTOPIA" from both sides + an insert leaflet.

-The excipients are: Microcrystalline Cellulose (Avicel PH 102), Crospovidone XL, Colloidal silicone dioxide (Aerosil 200), Magnesium Stearate, Hydroxypropyl methylcellulose (HPMC) E5, Polyethylene Glycol 6000, Talc, purified water, Titanium dioxide (C.I. 77891) and Colorant as follows:

  - For Blokatens HCT 5/25/160 mg FC Tablets: Ferric oxide yellow (C.I.77492)
  - For Blokatens HCT 10/12.5/160 mg FC Tablets: Ferric oxide red (C.I.77491)
  - For Blokatens HCT 5/12.5/160 mg FC Tablets: Ferric oxide yellow (C.I.77492)
  - For Blokatens HCT 10/25/160 mg FC Tablets: Ferric oxide red (C.I.77491)

- **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 Sieving, Blending, Compaction, Compression, Coating and Blistering.

-The manufacturing process was adequately validated according to relevant guidelines. Validation included validation of specific operating parameters for each step of manufacturing where applicable.

- **Control of Excipients**

-All excipients comply with comply with USP/BP.

- **Control of Drug Product**

-Product specifications include Description, Mass uniformity, Uniformity of Dosage Units test (by weight variation) for Valsartan and (by Content Uniformity (HPLC)) for Amlodipine & Hydrochlorothiazide, Dissolution of APIs, Identification of APIs (HPLC-DAD), Assay (HPLC), Related substances (HPLC) and Microbiological analysis.

-Analytical methods were revised and found to be suitable for the required testing.

-Batch Analysis from the proposed production site were provided for 3 batches for each strength. The results of all tests are well within specification limits and batch data is acceptable.

- **Stability**

-Stability data was submitted in (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 30°C ± 2°C, RH 65% ±5%). The finished pharmaceutical product is stable for 24 months if stored at or below 30°C.

- **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.

- **Summary basis of opinion:**

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

Drug substance (Amlodipine Besylate):

- Discussion about polymorphism, pH and hygroscopicity should be provided.
- Elemental analysis should be submitted to confirm the percentage of the elements comprising the structure of Amlodipine.
- XRPD test should be included in the API specification to confirm the polymorphic form of Amlodipine **otherwise** it should be tested in last time interval of long stability study to prove the stability of produced form.
- Elemental impurities risk assessment should be submitted.
- Genotoxic impurities risk assessment should be submitted.

- Nitrosamine impurities risk assessment should be submitted.
- Clarification for the control strategy of toluene and acetic acid, that may be carried over from the synthesis of the KSM to the final API, should be provided.
- Clarification for the control strategy of benzene to prevent its carry over to the final API, as a contaminant from the solvents used in the manufacturing process, should be provided.
- Justification for not testing the microbial limits and besylate content in the API should be provided.

Drug substance (Hydrochlorothiazide):

-The absence of microbiological testing from specification, batch analysis and stability should be justified.

Drug substance (Valsartan):

-Test results for the possible nitrosamines (NDMA, NDEA…, etc) in API should be submitted.

Drug product:

-Nitrosamine risk assessment for valsartan in the finished product should be submitted.

-The precautionary measures that should be taken during the manufacturing process due to photosensitivity of the API should be clarified.

-A second identification test according to the USP monograph and ICH Q6A should be added to the specifications.

-Water content test should be added to the specifications

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

Drug substance (Amlodipine Besylate):

- The supplier has provided discussion about polymorphism, pH and hygroscopicity.
- The supplier submitted results of XRPD in the last time interval of long-term stability study to prove the stability of produced form.
- The supplier has submitted Elemental impurities risk assessment.
- The supplier has submitted genotoxic impurities risk assessment.
- The supplier has submitted Nitrosamine impurities risk assessment.
- The supplier has submitted risk assessment of toluene and acetic acid proving that there's no risk of these solvents being carried over to the final API.
- The supplier has submitted risk assessment of benzene proving that there's no risk of benzene being carried over to the final API.
- The supplier has provided results of microbiological analysis in batches of the API and the results were consistently below the acceptance criteria which justifies the omission of microbial limits test from the specifications.

Drug substance (Hydrochlorothiazide):

- The supplier has provided discussion on the manufacturing process clarifying that it's incapable of supporting microbial growth which justified the omission of microbial limits from the specifications.

Drug substance (Valsartan):

- The supplier has provided test results for the possible nitrosamines (NDMA, NDEA…, etc) in six different batches of API and they were found below their detection or quantitation limits.

Drug product:

- The manufacturer has submitted risk assessment for the formation of Nitrosamine impurities in the finished pharmaceutical product. Moreover, the manufacturer has revised the specifications to include control for NDMA in the finished pharmaceutical product.
- The manufacturer has clarified the precautionary measures taken during the manufacturing process to protect the API from photosensitivity.
- The manufacturer has revised the specifications to include a second identification test as recommended by ICH Q6A.
- The manufacturer has revised the specifications to include Water content test.

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

-Amlodipine, Hydrochlorothiazide & Valsartan are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

-Amlodipine, Hydrochlorothiazide & Valsartan are indicated for indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including amlodipine, hydrochlorothiazide and the ARB class to which valsartan principally belongs.

Pharmacokinetics

Bioequivalence Study

- The bioequivalence study of Blokatens HCT 10/25/160 Film Coated Tablet from Utopia Pharmaceuticals relative to Exforge HCT 10/25/160 Film Coated Tablet administered to healthy participants.

Biowaiver

The EDA has granted a biowaiver for the lower strength Blokatens HCT 5/12.5/160 Film Coated Tablet, Blokatens HCT 5/25/160 Film Coated Tablet& Blokatens HCT 10/12.5/160, Film Coated Tablet based on the following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- All strengths of Amlodipine, Hydrochlorothiazide & Valsartan are manufactured by the same process.
- Amlodipine, Hydrochlorothiazide & Valsartan has linear pharmacokinetics over the therapeutic dose range.
- All tablets strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

An Open label single dose, randomized, two treatment, three sequence, Three periods, cross over bioequivalence study in healthy participants With a Washout Interval of Two Weeks Between Dosing in Healthy Participants.

Biological Samples Collection:

Before dosing Pre-dose, 0.33 hr. ,0.67 hr. ,1 hr. ,1.33 hr. ,1.67 hr. ,2 hr. ,2.33 hr.,2.67 hr.,3 hr., 3.33 hr.,3.67 hr.,4 hr.,4.5 hr.,5 hr.,6 hr.,7 hr.,8 hr.,9 hr., 10 hr., 12 hr., 24 hr., 36 hr., 48 hr. and 72 hr. post dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Amlodipine, Hydrochlorothiazide & Valsartan 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:

Results for Valsartan

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of Product name and strength under fast.

Treatment N=33	AUC_{0-t} ng.h/ml		$AUC_{0-\infty}$ ng.h/ml		C_{max} ng/ml		t_{max} h	$t_{1/2}$ h
Test	25313.789 (10159.269)		25733.888 (10231.478)		3483.029 (1446.002)		3.277	7.377
Reference	24182.889 (11236.051)	27192.386 (8354.8690)	24688.232 (11250.717)	27728.200 (8396.591)	3470.438 (1599.294)	3835.953 (1150.211)	3.131	8.1

***Ratio (90%) CI**	97.86 (87.10- 109.94)	97.40 (86.82- 109.27)	95.12 (82.60- 109.65)	NA	NA
CV (%)	35.400	35.827	34.240	NA	NA

*ln-transformed values

Results for Amlodipine

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t max (median, range) of Product name and strength under fast conditions.

Treatment N=33	**AUC0-72 ng.h/ml**		**Cmax ng/ml**		**tmax h**	**t1/2 h**
Test	207.790 (64.097)		6.139 (2.558)		7.364	39.128
Reference	268.597 (78.833)	208.329 (71.852)	5.341 (1.874)	5.947 (2.254)	6.912	38.78
***Ratio (90%) CI**	104.40 (100.73 -108.20)		107.43 (102.04- 112.75)		NA	NA
CV (%)	10.067		14.071		NA	NA

*ln-transformed values

Results for HCTZ

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t max (median, range) of Product name and strength under fast.

Treatment N=33	**AUC_{0-t} ng.h/ml**		**$AUC_{0-\infty}$ ng.h/ml**		**C_{max} ng/ml**		**t_{max} h**	**$t_{1/2}$ h**
Test	1069.287 (345.590)		1111.181 (352.044)		140.028 (39.788)		2.095	7.680
Reference	970.096 (301.070)	1005.062 (246.928)	1017.768 (311.127)	1051.377 (253.395)	133.269 (43.953)	128.235 (25.848)	2.176	7.76
***Ratio (90%) CI**	107.18 (101.22- 113.84)		106.37 (100.65-112.43)		106.78 (101.04- 112.85)		NA	NA
CV (%)	15.396		17.372		14.693		NA	NA

*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 Amlodipine 10mg, Hydrochlorothiazide 25mg &Valsartan 160mg in Blokatens HCT 10/25/160 Film Coated Tablet from Utopia Pharmaceuticals relative to Exforge HCT 10/25/160 Film Coated Tablet are Bioequivalent after a single oral dose of test and reference administration under Fasting on 33 participants.