EDA Assessment Report for human medicinal product

(Scientific Discussion)

Livtencity 200 mg Film Coated Tablets

(Maribavir)

Date: September, 2025.

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Livtencity 200 mg FCT from Takeda Scientific Office.

-The product is indicated to treat adults who have had an organ or bone marrow transplant and developed a CMV (‘cytomegalovirus’) infection that did not go away or came back again after taking another antiviral medicine.

II. Quality Aspect

Drug Substance

- Full details of the DS part have been submitted for evaluation.
- The drug substance Maribavir is white to off-white solid, non-hygroscopic, with pH-dependent aqueous solubility. At pH conditions of less than 7.5, the drug substance behaves as a weak base and its solubility decreases with increasing pH, it has low solubility with high permeability and classified as BCS class II, Maribavir also exhibits polymorphism with the commercial form being crystalline form VI.
- The synthesis of drug substance involves four stages. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via ^{1}H-NMR, ^{13}C-NMR, UV-spectroscopy, Mass Spectroscopy, IR-spectrometry, Elemental analysis and XRPD.
- The drug substance specifications are Description, Identification (IR & HPLC), Assay (HPLC), Related substances (HPLC), Residual solvents (GC), Sulphated ash, Particle size and Microbial limits.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results that demonstrated compliance with the current drug substance specification.
- The drug substance is packed in double low-density polyethylene (LDPE) bags and each bag is sealed with a plastic tie (with one bag inside the other) and the bagged drug substance is sealed in high-density polyethylene (HDPE) container. The proposed Container closure system is suitable to store drug substance and commonly used in the pharmaceutical industryand the specifications are acceptable.
- Stability of drug substance is submitted as (accelerated at 40°C, RH 75%) and (long term at 25°C, RH 60%), and conclude the conformity of specifications during the retest period of 60 months when stored at temperature between 15°C to 25°C.

Medicinal Product

- **Product Description**

-The finished product is an immediate release tablet including 200 mg Maribavir for oral administration. Livtencity 200 mg is a blue, film-coated, oval-shaped, convex tablet that is de-bossed with 'SHP' on one side and '620' on the other side. Each tablet is 15.5 mm in length, 7.8 mm in width, and 5.0 mm in thickness.

-The list of excipients is as follow:

-Tablet core: Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate.

-Film coating: Opadry II Blue 85F105081 which consists of Polyvinyl alcohol, Macrogol (polyethylene glycol), Titanium dioxide, Talc, Brilliant blue FCF aluminum lake (FD&C Blue #1) and Purified water.

- **Pharmaceutical development**

-The development of the product has been described, the choice of the dissolution method has also been justified & its discriminatory power has been demonstrated, the excipients are well known pharmaceutical ingredients, and their functions are explained.

-Overall, the choices of the packaging, manufacturing process, physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**

-The manufacturing process consists of blending, lubrication, compression and coating. The manufacturing process is considered a standard manufacturing process.

-It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

-The manufacturing process was adequately validated according to relevant guidelines. Validation included 3 consecutive production batches manufactured by the current manufacturer.

- **Control of excipients**

-All excipients comply with Ph. Eur. except for the non-compendial Opadry II Blue 85F105081 which complies to In-house specifications.

- **Control of drug product**

-Product specification includes Description, Identification (HPLC/PDA), Assay (HPLC), Related substances (HPLC), Uniformity of dosage units (HPLC), Dissolution and Microbial tests.

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

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

- **Container Closure System**

-The product is packed in 60 mL white, square high-density polyethylene bottle and a three-part 28 mm child resistant closure consisting of a polypropylene outer cap, inner cap and a foil laminate induction seal. The sealed bottles are labelled and placed within a paperboard folding carton.

- **Stability**

-Stability data was submitted in (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 30°C ± 2°C, RH 75% ± 5% and 25°C ± 2°C, RH 60% ± 5%), and conclude the conformity of specifications during the shelf life and storage conditions. The finished pharmaceutical product is stable for 36 months if stored at temperature not exceeding 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:**

-For Chemistry, Manufacture and Control aspects and based on the detailed review of CTD quality module. The quality of this product is considered to be acceptable & the product is approved.

III. Non-Clinical & Clinical Aspects

Introduction

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

Maribavir is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of refractory post-transplant CMV infection.

Maribavir belongs to a class of anti-cytomegalovirus antivirals called benzimidazole ribosides.3 It competitively inhibits the human CMV pUL97 viral protein kinase and disrupts CMV DNA replication and encapsidation, which results in viable but severely defective viruses, although the reasons for this remain poorly defined. In addition, maribavir also inhibits viral release from the nucleus to the cytoplasm by inhibiting pUL97-dependent phosphorylation of the nuclear lamina component lamin A/C, although the extent to which this activity contributes to its antiviral efficacy is unclear.

* List of Key Clinical Studies Supporting the Marketing Authorization of Livtencity 200 mg

- Study Titles:

- A Phase 2, Randomized, Dose-ranging Study to Assess the Safety and Anticytomegalovirus (CMV) Activity of Maribavir Versus Valganciclovir for Treatment of CMV Infections in Transplant Recipients Who Do Not Have CMV Organ Disease (SHP620-203).

- A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients (SHP620-302).
- A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients with Cytomegalovirus (CMV) Infections that are Refractory or Resistant to Treatment with Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir (SHP620-303).
- A Phase 2, Randomized Study to Assess the Safety and Anti- cytomegalovirus (CMV) Activity of Different Doses of Maribavir for Treatment of CMV Infections that are Resistant or Refractory to Treatment with Ganciclovir/Valganciclovir or Foscarnet in Transplant Recipients (SHP620-202).

*** Based on the key clinical studies of Livtencity 200 mg submitted to EDA, approval of the marketing authorization of the product is recommended.**