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)

Caspovitae, 50 mg Vial containing powder for concentrate for solution for IV infusion

(Caspofungin)

Date: September 2024

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Caspovitae 50 mg Vial containing powder for concentrate for solution for IV infusion from Pharma Solutions Egypt.

The product is indicated for:

- Treatment of invasive candidiasis in adult or pediatric patients.
- Treatment of invasive aspergillosis in adult or pediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult or pediatric patients.

II. Quality Aspects

Drug Substance

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is a white to off-white colour powder, is freely soluble in water and methanol, slightly soluble in ethanol. It shows polymorphs and the amorphous form is consistently produced by the supplier. It is hygroscopic in nature, and shows stereoisomerism.
- The synthesis of drug substance includes nine steps to produce through the formation of seven isolated intermediate. The two starting materials, all reagents, solvents & catalysts are well controlled.
- The drug substance is elucidated via FTIR spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy and the structure is well characterized. The polymorphism is confirmed via P-XRD.
- The drug substance specifications include the following tests: description, clarity & colour of solution, solubility, identification (by IR and HPLC), water content (Karl Fischer), sulphated ash, specific optical rotation, assay (HPLC), related substances (HPLC), acetic acid content (HPLC), ethylenediamine content (HPLC), residual solvents (by GC), benzene content (GC), microbiological tests and bacterial endotoxin test. All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 6 drug substance batches demonstrating compliance with the current drug substance specification.
- Container closure system is is suitable to store API and comply with food grade packaging material and the specifications are acceptable.

- Stability of API is submitted in accelerated (-70) ± 5°C and long term at (-18) ± 3 ºC storage conditions. The stability protocol includes the following tests: description, identification (HPLC), water content (Karl Fischer), assay (HPLC), related substances (HPLC), ethylenediamine content (HPLC), bacterial endotoxin limit and the study concluded the conformity of specifications during the shelf life and storage conditions.

Medicinal Product

- **Product Description**

Powder for concentrate for solution for infusion is a lyophilized sterile white to off-white powder to be reconstituted with water for injection and diluted prior to intravenous administration.
The product is packed in a 10 mL Type I glass vial with a butyl rubber stopper and an aluminum seal with a plastic flip-off cap with red button color.

The excipients are: sucrose, mannitol, carbon dioxide, concentrated Hydrochloric acid, sodium hydroxide and water for injection.

- **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 compounding, prefiltration, filtration, vials filling, lyophilization and sealing.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included the results for 3 batches comply with the current specifications.
- Control of excipients, all excipients comply with Ph. Eur. and the specifications of the excipients are acceptable.
- Product specifications include appearance, appearance of reconstituted solution, identification (by HPLC & UV), water content, pH, reconstitution time, extractable volume, uniformity of dosage units (mass variation), assay, related substances, particulate matter, sterility and bacterial endotoxin test. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for 3 batches (45 L) 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 in accelerated at 25±2ºC/60±5%RH and long term at 2°C-8°C storage conditions 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.

Summary basis of opinion:
From Chemistry, Manufacture and Control perspective, the main concern found during the evaluation process was as follow:
For the Drug product:
-The media fill report was missing.

The Quality of the drug product has been found satisfactory after:
-The applicant submitted media fill report which is revised and found satisfactory.

III. Non-Clinical Aspects

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

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

Caspofungin is indicated for to treat serious fungal infections, including candidemia (fungal infection in the blood), esophageal candidiasis (fungal infection of the esophagus), other candida infections, and aspergillosis (fungal infection in the lungs). It is also used to treat fungal infections assumed to be present in patients with febrile neutropenia

Pharmacodynamics

Caspofungin is an antifungal drug, and belongs to a new class termed the echinocandins. It is used to treat Aspergillus and Candida infection, and works by inhibiting cell wall synthesis. Antifungals in the echinocandin class inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-beta glucan synthase. There is a potential for resistance development to occur, however in vitro resistance development to Caspofungin by Aspergillus species has not been studied.

Mechanism of action

Caspofungin inhibits the synthesis of beta-(1,3)-D-glucan, an essential component of the cell wall of Aspergillus species and Candida species. beta-(1,3)-D-glucan is not present in mammalian cells. The primary target is beta-(1,3)-glucan synthase.

Pharmacokinetics

Absorption: 92% tissue distribution within 36-48 hours after intravenous infusion.

Protein binding: 97%

Metabolism: Metabolized slowly by hydrolysis and N-acetylation.

Route of elimination: After single intravenous administration of [3H] caspofungin acetate, excretion of caspofungin and its metabolites in humans was 35% of dose in feces and 41% of dose in urine.

Half-life: 9-11 hours.

Clearance: 12 mL/min [After single IV administration].

Bioequivalence Study

The bioequivalence study of Caspovitae, 50 mg Vial containing powder for concentrate for solution for IV infusion is not required as the test product is a parenteral formulation and therefore fulfils the exemption mentioned in bioequivalence guidelines* which state that "bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration".

***References**

1- Egyptian guideline for conducting bioequivalence studies for marketing authorization of generic products "Year 2023"

2-Guideline on the investigation of bioequivalence, committee for medicinal products for human use (CHMP) The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use, London, 20 January 2010, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.