COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Caspofungin Tillomed 50 mg and 70 mg powder for concentrate for solution for infusion (caspofungin acetate)

NL/H/5398/001-002/DC

Date: 07 October 2022

This module reflects the scientific discussion for the approval of Caspofungin Tillomed 50 mg and 70 mg powder for concentrate for solution for infusion. The procedure was finalised at 29 June 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Caspofungin Tillomed 50 mg and 70 mg powder for concentrate for solution for infusion, from Tillomed Pharma GmbH.

The product is indicated for:

- Treatment of invasive candidiasis in adult or paediatric patients;
- Treatment of invasive aspergillosis in adult or paediatric 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 paediatric patients.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Cancidas 50 mg and 70 mg powder for concentrate for solution for infusion which has been registered in the EEA by Merck Sharp & Dohme B.V. since 24 October 2001 through a centralised procedure (EMEA/H/C/000379)

The concerned member states (CMS) involved in this procedure were Austria, Denmark, Finland, France, Italy, Norway, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Caspofungine Tillomed is a powder for concentrate for solution for infusion. The powder is a white to off-white, compact power. After reconstitution, the solution is clear and colourless. Diluents for the final solution for infusion are sodium chloride solution for injection or lactated Ringer's solution.

Each vial of Caspofungine Tillomed 50 mg contains 50 mg caspofungin (as acetate). After reconstitution with 10.5 ml of water for injection, each ml of concentrate contains 5.2 mg caspofungin.

Each vial of Caspofungine Tillomed 70 mg contains 70 mg caspofungin (as acetate). After reconstitution with 10.5 ml of water for injection, each ml of concentrate contains 7.2 mg caspofungin.

Both strengths are packed in a 10 ml type 1 glass colourless single-dose vial with a 20 mm lyophilised grey rubber stopper and sealed with an aluminium flip-off seal with a plastic overseal (i.e. green for 50 mg and blue for 70 mg).

The excipients are sucrose, mannitol (E421), sodium hydroxide (E524) (to adjust the pH) and glacial acetic acid (E260).

II.2 Drug Substance

The active substance is caspofungin acetate, an established active substance not described in any pharmacopoeia. It is a white to off-white powder and freely soluble in water and N,N-dimethylformamide, soluble in methanol, sparingly soluble in ethanol and practically insoluble in ethyl acetate and acetonitrile. The substance exhibits polymorphism, a mixture of a crystalline and amorphous form is produced. The polymorphic form has no impact on drug product manufacture or performance.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The active substance is produced in five steps. The active substance is adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification has been established in-house by the MAH based on the specification of the ASMF holder and includes tests for description, specific rotation, identification, pH, water, clarity and colour of solution, residue on ignition, acetate, related substances, residual solvents, bacterial endotoxins, microbial limit and assay. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for six full scale batches stored at -70 ± 5°C (three batches for 36 months, three batches for 24, 12 and 9 months) and three batches stored at -20 ± 5°C (6 months) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 2 years with the storage condition "Preserve in tight, light-resistant containers. Store at -70°C ± 5°C".

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form, its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies consisted of quantification of the excipients and overfill by analyses of the reference product, determination of holding times and temperatures, compatibility with manufacturing materials, establishing fill volume and filtration and lyophilisation settings. The pharmaceutical development of the product has been adequately performed. The choice of manufacturing process is justified by the validation. The choice of the packaging is justified by the results of the stability studies.

Manufacturing process

The drug product is manufactured according to a standard process in six stages: preparation of a bulk solution by mixing and dissolution of all ingredients, followed by aseptic filtration, filling and partial stoppering of vials, lyophilisation, capping, visual inspection and packaging. The manufacturing process is adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full batches of each strength.

Control of excipients

The excipients comply with the corresponding Ph.Eur. monographs. These specifications are acceptable.

Microbiological attributes

The container closure system integrity is adequately demonstrated. The specifications of the container closure system and certificates of analysis comply with the relevant Ph.Eur. monographs. Adequate information on the container closure system was provided.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, physical evaluation, identity, reconstitution time, appearance of reconstituted solution, completeness of solution, clarity of solution, pH, water, container content, visible particles, sub-visible particles, bacterial endotoxins, sterility, related substances, uniformity of dosage units and assay. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life acceptance limits are almost identical, except for pH, water, related compound 2 and total impurities. The proposed release and shelf-life

specifications are acceptable. The provided risk evaluation regarding the presence of nitrosamine impurities in the drug product is sufficient, no risk was identified. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided from three full scaled batches of each strength, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three full scale batches of both strengths stored at 2°C - 8°C (24 months) and 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Under long term conditions almost all the tested parameters remain stable and within the proposed limits. The proposed shelf-life of 24 months and storage condition "Stored refrigerated at 2°C to 8°C" are justified. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. An adequate excursion stability study has been performed.

The concentrate which has been reconstituted with water for injection should be used immediately (see SmPC). Stability data have shown that the concentrate for solution for infusion can be stored for up to 24 hours when the vial is stored at 25°C or less.
The diluted patient infusion solution should also be used immediately. Stability data have shown that the product can be used within 24 hours when stored at 25°C or less, or within 48 hours when the intravenous infusion bag (bottle) is stored refrigerated (2 to 8°C) and diluted with sodium chloride solution 9 mg/ml (0.9 %), 4.5 mg/ml (0.45 %), or 2.25 mg/ml (0.225 %) for infusion, or lactated Ringer's solution.

From a microbiological point of view, the product should be used immediately once in use. If not used immediately, in-use storage times should not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution have taken place in controlled validated aseptic 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Caspofungin Tillomed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Caspofungin Tillomed is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cancidas which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Caspofungin acetate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Caspofungin Tillomed is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 Parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Caspofungin Tillomed is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Caspofungin Tillomed.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Increase in liver enzymes • Hypersensitivity reactions including histamine-mediated allergic reactions and SJS / TEN • Drug resistance • Drug interaction with rifampin and other inducers of drug clearance • Drug interaction with cyclosporine • Drug interaction with tacrolimus
Important potential risks	• None
Missing information	• Exposure during pregnancy • Additional data on the safety and effectiveness in neonates and infants < 3 months of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cancidas. No new clinical studies or bioequivalence studies were conducted. The MAH demonstrated that the quantitative composition of Caspofungin Tillomed is entirely the same as the reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflets (PL) has been performed on the basis of a bridging report making reference to Caspofungin Cadiasun 50 mg powder for concentrate for solution for infusion (NL/H/3523/001) for both the 50 mg and 70 mg product leaflets for Caspofungin Tillomed. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflets.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Caspofungin Tillomed 50 mg and 70 mg powder for concentrate for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Cancidas 50 mg and 70 mg powder for concentrate for solution for infusion. Cancidas is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Caspofungin Tillomed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 June 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A