LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kaspofungin Lorien
(caspofungin (anhydrous), caspofungin acetate)

SE/H/2434/001-002/DC

This module reflects the scientific discussion for the approval of Kaspofungin Lorien. The Public Assessment Report was written in (February 2017) by the previous RMS (NL) after initial procedure NL/H/3562/001-002/DC and is attached at the end of this document. RMS transfer from (NL) to SE was completed 07-09-2023. For information on changes after this date please refer to the module 'Update'.

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Active substance	caspofungin (anhydrous)
Pharmaceutical form	Powder for concentrate for solution for infusion
Strength	50 mg: 70 mg
Applicant	Laboratorios Lorien S.L.
EU-Procedure number (original)	NL/H/3562/001-002/DC

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

C B G

M E B

Public Assessment Report

I. SCIENTIFIC DISCUSSION

Caspofungine Regiomedica 50 mg and 70 mg, powder for concentrate for solution for infusion

(caspofungin acetate)

NL/H/3562/001-002/DC

II. DATE: 16 FEBRUARY 2017

This module reflects the scientific discussion for the approval of Caspofungine Regiomedica 50 mg and 70 mg, powder for concentrate for solution for infusion. The procedure was finalised on 27 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

II.1 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

II.2 I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Caspofungine Regiomedica 50 mg and 70 mg, powder for concentrate for solution for infusion, from Regiomedica 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, neutropaenic 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 product Cancidas 50 mg and 70 mg powder for concentrate for solution for infusion (EU/1/01/196/001) which has been registered by a centralised procedure in the EEA by Merck Sharp & Dohme since 24 October 2001.

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Spain, Finland, France, Italy, Norway, Sweden and the United Kingdom

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

II.3 II. QUALITY ASPECTS

II.3.1 II.1 Introduction

Caspofungine Regiomedica 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, colourless, to slightly yellow. Diluents for the final solution for infusion are sodium chloride solution for injection or lactated Ringer's solution.

Each vial of Caspofungine Regiomedica 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 Regiomedica 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.

The powder for concentrate for solution for infusion is packed in type I glass vials with a bromobutyl stopper and a aluminum flip-off cap.

The excipients are sucrose, mannitol (E421), succinic acid (E363) and sodium hydroxide (E524) (for pH adjustment).

II.3.2 II.2 Drug Substance

The active substance is caspofungin acetate, an established active substance not described in any Pharmacopoeia. The active substance is a white to off-white powder. It is freely soluble in water and methanol and slightly soluble in ethanol. The substance exhibits polymorphism, only one polymorphic form is produced by the active substance manufacturer.

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.

II.3.2.1 Manufacturing process

The active substance is produced in 5 steps. The active substance is adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

II.3.2.2 Quality control of drug substance

The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. The specification is acceptable in view of the route of synthesis and, except for the control of any individual impurities, various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

II.3.2.3 Stability of drug substance

Stability data on the active substance have been provided for 7 batches stored at -70±10°C (up to 48 months) and 2 full scale batches at -20±5°C (up to 36 months). At -70°C a tendency for an increase in two impurities and hence in total impurities has been seen during storage. At -70°C a tendency for an increase in two impurities and hence in total impurities is seen during storage. For the primary batches a high initial level of an impurity was seen, which was decreased after 3 months and thereafter remained almost unchanged. At -20°C there is a tendency for an increase in any individual unknown impurity, which is not seen at -70°C. Increase to a level above the proposed specification limit is seen after 24 months. Therefore, based on the data submitted, a retest period could be granted of 48 months and storage condition 'in original containers at -70 ± 10°C' are justified.

II.3.3 II.3 Medicinal Product

II.3.3.1 Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies consist of the selection of a buffering agent, a similarity analysis with the reference product and development of the lyophilisation cycle. 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.

II.3.3.2 Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and consists of 5 stages, namely preparation, filtration, filling, lyophilisation and sealing/packaging. Process validation data on the product have been presented for 3 full scaled batches in accordance with the relevant European guidelines.

II.3.3.3 Control of excipients

All excipients except succinic acid comply with the corresponding Ph.Eur. monographs. The in-house specification for succinic acid is based on the United States Pharmacopeia. These specifications are acceptable.

II.3.3.4 Microbiological attributes

The drug product microbiological tests are conducted at batch release, production process and during the stability period and meet the requirements given for sterile products in the Ph. Eur. The container closure integrities for the finished products have been validated by bacterial immersion testing using the relevant primary packaging materials for the presentation. The validation results display the suitability of primary packaging to protect the drug product from any microbial ingress. The container closure integrity is also monitored through sterility testing in the submission batches and covered by the commercial stability protocols. No data on the container closure integrity testing in order demonstrate adequate prevention of microbial contamination is provided. However, because integrity testing is routinely performed as part of the manufacturing process, no objection will be made.

II.3.3.5 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, identity, constituted solution (completeness and clarity, visible particles), pH, water, related substances, assay, uniformity of dosage units, bacterial endotoxins, sterility, subvisible particles and color of solution. The proposed release and shelf-life acceptance limits are almost identical, except for assay, related substances and water content. The inuse specification is acceptable and includes control of appearance, colour of solution, assay, related substances, osmolality, pH, particulate matter, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

II.3.3.6 Stability of drug product

Stability data on the product have been provided for 3 full scaled 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. The batches were stored in the proposed packaging. Under accelerated conditions two of the tested parameters exceed the proposed limits. The product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months when stored and transported refrigerated (2°C-8°C). In-use stability data has been provided, demonstrating that the product remains stable for 24 hour following reconstitution when stored at 25°C. The further diluted product is demonstrated to remain stable for 24 or 48 hours in-use, when stored at 25°C or less or at 2°C - 8°C respectively.

II.3.3.7 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.3.4 II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Caspofungine Regiomedica 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.

II.4 III. NON-CLINICAL ASPECTS

II.4.1 III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Caspofungine Regiomedica 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.

II.4.2 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-todate 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.

II.5 IV. CLINICAL ASPECTS

II.5.1 IV.1 Introduction

Caspofungine acetrate 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.

II.5.2 IV.2 Pharmacokinetics

Caspofungine Regiomedica 50 mg and 70 mg, powder for concentrate for solution for infusion are parenteral formulations 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 Caspofungine Regiomedica 50 mg and 70 mg, powder for concentrate for solution for infusion 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.

II.5.3 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 Caspofungine Regiomedica.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Increase in liver enzymes - Histamine-mediated allergic reactions (hypersensitivity and anaphylaxis) - Drug resistance (lack of efficacy against less common noncandida yeasts and non-aspergillus moulds)

	- Drug interaction with rifampicin and other inducers of drug clearance - Drug interaction with cyclosporine - Drug interaction with tacrolimus
Important potential risks	- Use in patients with fructose intolerance or sucrose-isomaltase insufficiency
Missing information	- Exposure during pregnancy and lactation - Use in neonates and infants below 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.

II.5.4 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 were conducted. The MAH was not required to demonstrate through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

II.6 V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. In the study it has been assessed whether potential users could locate, understand and appropriately act upon the information contained in the leaflet. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

II.7 VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Caspofungine Regiomedica 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 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.

In the Board meeting of 25 August 2016, the in-use stability period was discussed. After tightening of limits, the issue was considered resolved.

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 Caspofungine Regiomedica with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 September 2016.

II.7.1 STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached