Public Assessment Report
Scientific discussion

Caspofungin Orion
(caspofungin)

SE/H/1543/01-02/DC

This module reflects the scientific discussion for the approval of Caspofungin Orion. The procedure was finalised on 2016-12-08. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Caspofungin Orion, 50 mg and 70 mg, Powder for concentrate for solution for infusion, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cancidas, 50 mg, powder for concentrate for solution for infusion, authorised in EU since 2001, with Merck Sharp & Dohme Ltd as marketing authorisation holder.

Similarity to medicinal products with orphan drug status

According to Article 8.1 of Regulation (EC) No 141/2000, where a marketing authorization in respect of an orphan medicinal product is granted, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorization, or grant a marketing authorisation, accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product (so-called 10 year market exclusivity).

The Applicant has completed module 1.7.1 (similarity) and claim that Caspofungin Orion is not similar to Cresemba (isavuconazonium). The claim of non similarity should be based on the comparison with the molecular structural features, mechanism of action and therapeutic indications, as defined in the Article 3 of Regulatory (EC) No 847/2000.

The RMS agrees with the Applicant that Caspofungin Orion is not similar to Cresemba (isavuconazonium).

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.
II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Caspofungin is extensively bound to albumin. Caspofungin undergoes spontaneous degradation to an open ring compound. Further metabolism involves peptide hydrolysis and N-acetylation. Two intermediate products, formed during the degradation of caspofungin to this open ring compound, form covalent adducts to plasma proteins resulting in a low-level, irreversible binding to plasma proteins. The elimination of caspofungin from plasma is slow with a clearance of 10-12 ml/min. Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour intravenous infusions. A short alpha-phase occurs immediately post-infusion, followed by a beta-phase with a halflife of 9 to 11 hours. An additional gamma-phase also occurs with a half-life of 45 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. Caspofungin displays moderate non-linear pharmacokinetics with increased accumulation as the dose is increased, and a dose dependency in the time to reach steady state upon multiple-dose administration.

No bioequivalence study has been submitted. The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. The applied product also contains the same excipients as the reference product. None of the excipients are known to interact with the drug substance. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1). Thus, the absence of bioequivalence studies is acceptable.
IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Orion.

Safety specification

Summary table of safety concerns as proposed in RMP:

| Important identified risks                                                                 | • Serious hypersensitivity reactions |
|                                                                                         | • Increased caspofungin AUC in adult patients with moderate hepatic impairment |
|                                                                                         | • Increased liver enzymes when used concomitantly with cyclosporine |
| Important potential risks                                                              | • Hepatotoxicity |
| Missing information                                                                     | • Administration in pediatric patients with any degree hepatic impairment or adult patients with severe hepatic impairment |
|                                                                                         | • Administration during pregnancy or breast-feeding |

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Caspofungin Accord 50 mg powder for concentrate for solution for infusion, (EU/1/15/1081/001-002; EMEA/H/C/004134). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Caspofungin Orion, is found adequate. There are no objections to approval of Caspofungin Orion, from a non-clinical and clinical point of view. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Caspofungin Orion, 50 mg and 70 mg, Powder for concentrate for solution for infusion was positively finalised on 2016-12-08.
# Public Assessment Report – Update

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
</tr>
</thead>
</table>

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