Public Assessment Report
Scientific discussion

Caspofungin Idifarma Desarrollo Farmacéutico 50 mg and 70 mg powder for concentrate for solution for infusion

Caspofungin Acetate

ES/H/0336/01-02/DC

Applicant: Idifarma Desarrollo Farmacéutico, S.L.

This module reflects the scientific discussion for the approval of **Caspofungin Idifarma Desarrollo Farmacéutico 50 mg and 70 mg powder for concentrate for solution for infusion.** The procedure was finalised on June 2016. For information on changes after this date please refer to the module "Updateò

INTRODUCTION

This decentralised application concerns a generic version of caspofungin acetate, under Caspofungin Idifarma Desarrollo Farmacéutico 50 mg and 70 mg powder for concentrate for solution for infusion trade names.

The originator product is Cancidas® 50 mg and 70 mg powder for concentrate for solution for infusion (Merck Sharp & Dohme Limited, UK), which was granted marketing authorisation in EU through a centralised procedure on October 24th, 2001 (EU/1/01/196/001-002).

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member States involved in this procedure are:

ES/H/0336/01-02/DC: LU

Caspofungin is indicated for various fungal infections, in Europe for the treatment of:

- Invasive candidiasis in adult or paediatric patients,
- Invasive aspergillosis in adult patients or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole,
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropaenic adult or paediatric patients.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Caspofungin Idifarma Desarrollo Farmacéutico 50 mg and 70 mg powder for concentrate for solution for infusion**.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

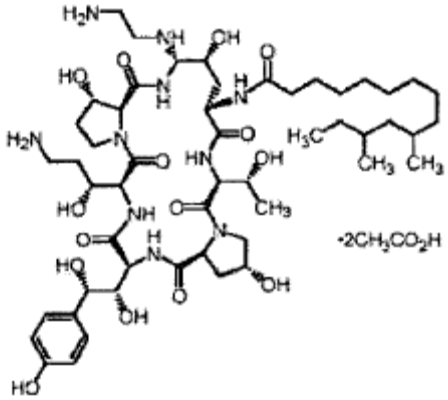
II.1 Introduction

Caspofungin Idifarma Desarrollo Farmacéutico 50 mg Powder for Concentrate for Solution for Infusion is packaged in a 10 ml Type I glass vial with a grey rubber bromo-butyl stopper and a red flip-off aluminium cap. The product is supplied in packs of 1 vial.
Each vial of Caspofungin Idifarma Desarrollo Farmacéutico 50 mg Powder for Concentrate for Solution for Infusion contains caspofungin acetate equivalent to 50 mg caspofungin.
Caspofungin Idifarma Desarrollo Farmacéutico 70 mg Powder for Concentrate for Solution for Infusion is packaged in a 10 ml Type I glass vial with a rubber bromo-butyl stopper and a yellow flip-off aluminium cap. The product is supplied in packs of 1 vial.
Each vial of Caspofungin Idifarma Desarrollo Farmacéutico 70 mg Powder for Concentrate for Solution for Infusion contains caspofungin acetate equivalent to 70 mg caspofungin.
Other ingredients consist of the pharmaceutical excipients, namely sucrose, mannitol, glacial

acetic acid and sodium hydroxide.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Caspofungin acetate
Chemical name(s): 1-[(4R,5S)-5-[(2-aminoethyl)amino]-N2-(10,12-dimethyltetradecanoyl)-4-hydroxy-L -ornithyl-L-threonyl-trans-4-hydroxy-L-prolyl-(S)-4-hydroxy-(p-hydroxyphenyl)-L-threonylthreo-3-hydroxy-L-ornithyltrans-3-hydroxy-L-proline cyclic (6R1)- peptide, diacetate salt
Structure:



Molecular formula: C52H88N10O15 . 2 C2H4O2
Molecular weight: 1213.43 g/mol (as diacetate salt)
Appearance: White to off-white powder.
Solubility: Freely soluble in water and methanol and slightly soluble in ethanol.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance caspofungin acetate. Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate globally acceptable and stable products that could be considered generic medicinal products of the currently licensed products,

Cancidas 50 mg and 70 mg Powder for Concentrate for Solution for Infusion (Merck Sharp and Dohme Limited).
A satisfactory account of the pharmaceutical development has been provided.
All excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on three production scale batches of each strength of the finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification.
Information about the reference standards is provided.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.
The results from these studies support a shelf-life of 18 months for the unopened vial, with the special storage precaution of ñStore in a refrigerator (2°C - 8°C)ò.
Chemical and physical stability has been demonstrated for the reconstituted concentrate for 24 hours at 25°C.
Chemical and physical stability has been demonstrated for the diluted solution for infusion for 24 hours at 25°C and for 48 hours at 2 to 8°C when diluted with sodium chloride solution 9 mg/ml (0.9%), 4.5 mg/ml (0.45%), or 2.25 mg/ml (0.225%), or lactated Ringerôs solution.
Chemical and physical in-use stability has been demonstrated for 24 h hours at 25°C before its use.
From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution have taken place in controlled validated aseptic conditions.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.
The submitted application concerns Powder for Concentrate for Solution for Infusion with the active substances in the same form as the reference product.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

An ERA was submitted. The log Kow determined experimentally is below the threshold 4.5 defined by the EMEA/CHMP/SWP/4447/00 Guideline. In Phase I, the value predicted environmental concentration in suface water (PECSURFACEWATER) is lower than the 0.01 µg/L limit that would require Phase II environmental fate an effect analysis to be conducted. Consequently, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

II.3 Clinical aspects

Introduction

Caspofungin acetate is well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

For this generic application, the MAH has not submitted a bioequivalence study, which is discussed below.

Biowaiver

The Applicant did not conduct any clinical study to support this application. According to the Guideline on the investigation of bioequivalence, if the test product is an aqueous intravenous solution at time of administration and contains an active substance (caspofungin acetate) in the same concentration as an approved intravenous solution, bioequivalence studies may be waived. The Applicant claims that a bioequivalence study is not required since this medicine contains the same active substance in the same quantity as the reference product and has the same indications, route of administration, dosage form and posology. Further, it contains the same inactive excipients in similar amounts. This data is not shown for confidentiality reasons.

Clinical bioequivalence studies are not necessary in view that both, the reference product and the proposed product are aqueous intravenous solution containing the same active substance as the currently approved product. There were no qualitative differences in excipients and the quantitative differences are not expected to affect the bioavailability between both products.

Bioequivalence

Not Applicable (see above)

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Efficacy and safety of the active substance caspofungin acetate is well documented for the reference medicinal product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the submitted evidence Caspofungin Idifarma Desarrollo Farmacéutico 50 mg and 70 mg powder for concentrate for solution for infusion can be considered equivalent to Cancidas® 50 mg and 70 mg powder for concentrate for solution for infusion (Merck Sharp & Dohme Limited, UK).

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in June 2016.