17 December 2015
EMA/32587/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Caspofungin Accord

International non-proprietary name: caspofungin

Procedure No. EMEA/H/C/004134/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ASMF	Active Substance Master File
CHMP	Committee for Medicinal Products for Human use
cfu	Colony Forming Units
CQA	Critical Quality Attribute
EC	European Commission
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
IV	Intra-venous
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
NMT	Not more than
Ph. Eur.	European Pharmacopoeia
ppm	parts per million
QTPP	Quality target product profile
RRT	Relative retention time
SmPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
UV	Ultraviolet
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 6 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Caspofungin Accord, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: CANCIDAS, 50 mg and 70 mg, powder for concentrate for solution for infusion
  - Marketing authorisation holder: Merck Sharp & Dohme Ltd, United Kingdom
  - Date of authorisation: 24-10-2001
  - Marketing authorisation granted by:
    - Community
      Community Marketing authorisation number: EU/1/01/196/001 (50 mg); EU/1/01/196/003 (70 mg)
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: CANCIDAS, 50 mg and 70 mg, powder for concentrate for solution for infusion
  - Marketing authorisation holder: Merck Sharp & Dohme Ltd, United Kingdom
  - Date of authorisation: 24-10-2001
  - Marketing authorisation granted by:
    - Community
      Community Marketing authorisation number: EU/1/01/196/001 (50 mg); EU/1/01/196/003 (70 mg)

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

N/A (this medicinal product is a parenteral preparation. Therefore a bioequivalence study is not applicable according to CPMP/EWP/QWP/1401/98 Rev.1)

Information on paediatric requirements

Not applicable

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 6 March 2015.
- The procedure started on 26 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 September 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 8 October 2015.
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 November 2015.
- Rapporteur assessment report on the responses provided by the applicant, dated 1 December 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 3 December 2015.
- During the meeting on 17 December 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Caspofungin Accord.

2. Scientific discussion

2.1. Introduction

Caspofugin acetate is a semi-synthetic lipopeptide that belongs to the relatively new class of antifungal agents called the echinocandin family. Caspofungin blocks, through non-competitive inhibition of the enzyme β(1,3)-D-glucan synthase, the synthesis of the fungal cell wall component β(1,3)-D-glucan which is essential for the cell wall synthesis of numerous fungal species and yeasts, but is absent in mammalian cells.

The reference product Cancidas (EU approval 24 October 2001) is marketed worldwide and is indicated for various fungal infections, in Europe for the:

- 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 (AmB), lipid formulations of AmB and/or itraconazole, and
- Empirical therapy for presumed fungal infections (e.g. Candida or Aspergillus) in febrile, neutropenic adult or paediatric patients.

Accordingly, the safety and efficacy of caspofungin have been shown in several clinical trials in these indications for the reference medicinal product. Additionally, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

Both the Caspofungin Accord and the originator product Cancidas are intended for intravenous use and must be reconstituted and further diluted prior to use.

Caspofungin Accord should be given as a single daily infusion administered as slow intravenous infusion over approximately 1 hour.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 50 or 70 mg of caspofungin (as diacetate salt) as active substance.

Other ingredients are sucrose, mannitol, succinic acid and sodium hydroxide.

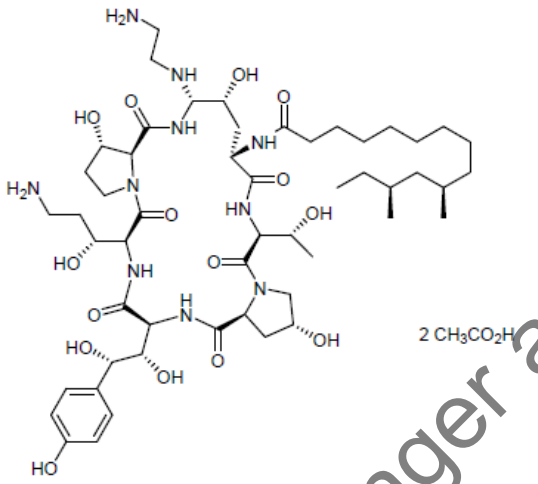
The product is available in type I clear glass vials with bromobutyl rubber stoppers and red or orange aluminium seals with transparent plastic flip off buttons as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on caspofungin acetate is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of caspofungin acetate is 1-[(4*R*,5*S*)-5[(2-aminoethyl)amino]-*N*2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-*L*-ornithine]-5-[(3*R*)-3-hydroxy-*L*-ornithine]pneumocandin Bo diacetate or (4*R*,5*S*)-5-((2-aminoethyl)amino)-*N*(2)-(10,12-dimethyltetradecanoyl)-4-hydroxy-*L*-ornithyl-*L*-threonyl-trans-4-hydroxy-*L*-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-*L*-threonyl-threo-3-hydroxy-*L*-ornithyl-trans-3-hydroxy-*L*-proline cyclic (6-1)-peptide. It has the molecular formula $C_{56}H_{96}N_{10}O_{19}$ corresponding to a relative molecular mass of 1213.42 g/mol and it has the following structure:



The structure of caspofungin acetate was elucidated by a combination of 1D and 2D ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, LCMS/MS and elemental analysis. Comparison of IR, UV and HPLC spectra with those of the reference product provided further proof of structure.

Caspofungin acetate is a white to off-white hygroscopic amorphous powder and is freely soluble in water. It is sensitive to humidity and heat but is not photosensitive. The finished product is a lyophilised powder which is produced under conditions which minimise degradation.

Caspofungin acetate contains 16 chiral centres. Of these, 15 are controlled in the constituent amino acids and by the fermentation process. The final centre is introduced selectively in the final step of the synthetic process. Only two of the chiral centres are at all chemically labile which would result in diastereomers, detectable by HPLC. A test for specific optical rotation is included in the active substance specifications. Polymorphism has not been observed for caspofungin acetate and it is only known in the amorphous form.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Three manufacturers are involved in the production of Caspofungin. The first two carry out a fermentation with different processes and on different scales to produce an intermediate. The third manufacturer then converts the intermediate into the active substance, the quality of which is equivalent, irrespective of which fermentation process is used. The starting materials were re-defined during the procedure at the request of CHMP in order to ensure the quality of the active substance throughout the product lifecycle.

A series of purification steps are carried out to remove impurities and ensure the purity of the active substance. Stereochemistry originates in the raw material inputs and is controlled by the organism during

fermentation. Stereochemistry at the aminal centre is maintained during the final substitution reaction under substrate control.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and considered satisfactory. Potential and actual impurities were well discussed with regards to their origin and characterised. The purge of catalyst residues is ensured by the heavy metals and elemental impurities tests in the active substance specification. Adequate purge of reagents and their by-products has been demonstrated.

The active substance is packaged in a laminated aluminium bag, sealed by heat welding, and stored inside a second identical bag. The materials comply with EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC-UV (caspofungin and acetate), specific optical rotation), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), elemental impurities (ICP-MS), pH (Ph. Eur.), residual solvents (GC), related substances (HPLC), water content (KF), acetate content (HPLC-UV), assay (HPLC) and microbiological quality (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were either set at levels equivalent to the originator active substance or qualified by toxicological studies and appropriate specifications have been set. Acceptance criteria for heavy metals elemental impurities ensure adequate purge of metal catalysts and appropriate levels have also been set for residual solvents used in the synthetic process.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three production scale batches of active substance made with intermediate from both sources was provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale batches of caspofungin acetate from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (-80 ± 10 °C) and for up to 6 months under accelerated conditions (-20 ± 5 °C) according to the ICH guidelines were provided. The following parameters were tested: appearance, water content, related substances and assay. The analytical methods used were the same as for release and were stability indicating. All tested parameters were well within specification at all time-points and no significant trends were observed.

Forced degradation studies were carried out in solution and in the solid state. Solid caspofungin acetate is very sensitive to heat and humidity whilst in solution, degrading under both acidic and basic conditions. Photostability testing following the ICH guideline Q1B was also performed on one batch and the active substance shown not to be photosensitive.

A further study on one batch stored at 5 ± 3 ^{o}C showed that the active substance is stable at this temperature for up to one month. Thus, short term temperature excursions during shipping should not affect the quality of caspofungin acetate.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored in the proposed container at -80 ± 10 °C.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of development was to develop a finished product equivalent to that of the reference medicinal product, Cancidas. Accordingly, the quality target product profile (QTPP) was defined following analysis of Cancidas as a lyophilised powder for concentrate for solution for IV infusion with the same active substance and excipient content, appearance and container that meets compendial and other relevant quality standards for assay, purity, microbial quality and is stable over a suitable shelf-life. Critical quality attributes (CQAs) identified were sterility, appearance and reconstitution characteristics, assay, purity and stability.

Caspofungin acetate is highly soluble in aqueous media but sensitive to heat, oxygen and extremes of pH. Optimum stability is achieved between pH 5 and 7. In order to ensure stability during compounding and reconstitution, as well as suitable osmolarity, a series of buffers was examined. Succinic acid was chosen since, out of those investigated, it has the best buffering capacity between pH 5.5 and 6.5, results in less degradation, and produces a reconstituted solution of suitable osmolarity for infusion. It also enables production of a satisfactory cake following lyophilisation.

Other than the buffering agent, the composition is quantitatively and qualitatively identical to that of Cancidas. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or other relevant standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

During manufacture, compounding is carried out at 2-8 ^{o}C under an argon atmosphere with the exclusion of oxygen to minimise degradation. Stirrer speed is limited to prevent foaming. The unrefrigerated holding time between compounding and lyophilisation is appropriately controlled. Excipients are dissolved first and pH adjusted to 5.5-5.7 which minimises the compounding time of the active substance and results in a final bulk solution of pH 5.9-6.1. Each vial is over-filled in order to enable extraction of 10 ml of reconstituted solution containing the required (5.2 or 7.2 mg/ml depending on the strength/dose) concentration. Limits for the filling process have been set based on the equipment capability and assay limits of the finished product. Appropriate limits have also been set for compounding, filling and overall processing times in order to minimise degradation.

Temperature and pressure at various stages of the lyophilisation process were optimised in order to ensure an adequate cake appearance, prevent collapse, and minimise the formation of degradants.

The entire process is carried out aseptically since the finished product is both heat and oxygen sensitive and thus not compatible with terminal sterilisation. Seal integrity was demonstrated, thus preventing oxygen or moisture ingress throughout shelf-life.

The primary packaging is a type I clear glass vial with bromobutyl rubber stopper and aluminium seal with transparent plastic flip off button. The materials comply with Ph. Eur. and EC requirements. The container closure system chosen is similar to that of the reference medicinal product. Compatibility with the materials

has been demonstrated, in particular, with the rubber stopper. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps carried out aseptically: compounding; sterile filtration; filling; lyophilisation; sealing. The compounding is carried out under a continuous flow or argon with checks for dissolved oxygen and pH before addition of the active substance. The process is considered to be a non-standard manufacturing process.

The applicant originally proposed to manufacture the product on two separate scales. The process has been validated on three consecutive batches of each strength at the smaller scale. However, the larger scale process has not yet validated and being a non-standard process, this is not considered acceptable. Therefore, only the smaller scale can be used commercially until full validation on the larger scale has been performed. The larger proposed manufacturing scales will need to be applied for post-authorisation.

It has been demonstrated that the smaller scale manufacturing processes are capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this aseptic process, given the sensitivity of the active substance.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance, identification (IR, HPLC), pH of solution (Ph. Eur.), completeness, clarity and colour of solution (Ph. Eur. or in-house methods), water content (KF), assay (HPLC), related substances (HPLC), deliverable volume (Ph. Eur.), particulate contamination (Ph. Eur.), uniformity of dosage units (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). Several degradation products and water content increase during storage and therefore, limits are different for release and during shelf-life. Nonetheless, these limits are appropriate since the impurities are either known *in vivo* metabolites or toxicologically qualified.

Separate in-use shelf life specifications have been provided with wider limits for impurities given that these parameters were outside of specification following reconstitution (see stability section for details).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three production scale batches of each strength stored for up to 18 months (50 mg) or for up to 24 months (70 mg) under long term conditions (5 ± 3 °C) and for up to 6 months under accelerated conditions (25 °C / 60% RH) in line with the ICH guidelines was provided. The batches of finished product are identical to and packed in the same primary packaging as those proposed for marketing and were stored either upright or inverted. Samples were tested for appearance, pH of solution, completeness, clarity and colour of solution, water content, assay, related substances, particulate contamination, sterility and bacterial

endotoxins. A trend of increasing impurities was observed for both strengths although the levels were well within the specifications at the latest time-point. Water content appears to increase initially but is then stable or decreases. Therefore, the wider limits for impurities, assay, and water content in the shelf-life specifications are justified.

In addition, one batch of the 70 mg presentation was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No differences were observed between the exposed sample and a control sample stored in the dark. Thus, Caspofungin Accord is not photosensitive. Forced degradation studies were carried out in the solid state (exposure to heat) and in solution (exposed to acid, base, oxidant and heat). Significant degradation was seen under all conditions *via* different pathways.

In-use stability studies were carried out on the 70 mg vial as this was shown to be the worst case scenario in terms of degradation. The product was treated according to the administration instructions in the SmPC (section 4.2). Following reconstitution as a concentrate with either 0.9% saline solution or lactated Ringer's solution, two impurities increase over time. One is a hydrolysis product and *in vivo* metabolite, the other a dimer. On subsequent dilution into infusion bags, the amount of hydrolysis product continues to increase whilst the amount of dimer decreases. The levels of impurities are higher than stated in the release and shelf-life specifications. Therefore, separate in-use shelf life specifications have been provided with wider limits for impurities. This is considered acceptable and an in-use shelf-life of 24 hours at 25 ^{o}C for the concentrate and 24 hours at 25 ^{o}C or 48 hours refrigerated for the diluted solution is acceptable, notwithstanding microbiological recommendations as stated in the SmPC (section 6.3).

Based on available stability data, the proposed shelf-life 2 years stored in a refrigerator at 5 ± 3 °C as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Due to the inherent instability of the active substance, precautions have been taken in terms of storage conditions, and in-use stability specifications have been provided.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Caspofungin Accord manufactured by Accord Healthcare Ltd. is considered unlikely to result in any significant increase in the combined sales volumes for all caspofungin containing products and the exposure of the environment to the active substance. CHMP agreed that the risk for the environment is not expected to be increased.

2.3.3. Toxicology

Excipients

The excipients used in Caspofungin Accord are commonly used in oral products. With exception of the buffering agent succinic acid, the excipients are the same as for the originator Cancidas (MSD). Thus, no toxicological qualification is considered necessary.

Impurities

Compared to the reference product Cancidas (MSD), higher levels for identified drug product impurities have been proposed.

Impurity B is the primary degradation product of caspofungin, but also the major systemic human metabolite. Consequently, this impurity can be accepted at levels exceeding specifications for Cancidas without any further toxicological qualification.

Impurity C is a degradation product of caspofungin formed by reaction of two caspofungin molecules with each other. The Applicant has performed a safety assessment based on results from non-clinical studies conducted previously with the reference product Cancidas (MSD) in order to justify the proposed limits. This was considered acceptable by CHMP.

A genotoxicity evaluation of caspofungin acetate impurities and raw materials did not identify any alerting structures.

Impurity at RRT 1.23 is a degradation product formed only in solid state and only in lyophilized product when it is exposed to heat. This impurity is controlled according to ICH Q3B (R2), although fermentation products are not covered by the scope of Q3B. This was considered acceptable by CHMP.

2.3.4. Discussion on non-clinical aspects

Qualification of impurities

Despite some uncertainty with respect to the levels of impurity C in the batches used for Cancidas toxicity testing, based on the batch results and the maximum allowed level, accordingly an appropriate shelf life limit was considered acceptable by CHMP. See quality part of the assessment with regard to the in-use stability specification for this impurity.

2.3.5. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Caspofungin Accord and justifications that it does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non- clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Caspofungin Accord powder for concentrate for solution for infusion containing caspofungin acetate.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of caspofungin based on published literature. The SmPC of Caspofungin Accord is in line with the SmPC of the reference product Cancidas.

Exemption

This marketing authorisation application for Caspofungin Accord powder for concentrate for solution for infusion is, as previously mentioned, submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended for 50 mg and 70 mg strengths.

Biowaiver

No bioequivalence studies have been conducted. The applicant claims that bioequivalence studies are not required for this application, as Caspofungin Accord (50 mg and 70 mg powder concentrate for solution for infusion) is caspofungin medicinal product for preparation of an aqueous intravenous solution containing the same active substance in the same concentration as the reference product Cancidas (50 mg and 70 mg). Further, CHMP noted the Applicant statement that none of the excipients in the infusion solution prepared by Accord interact with or affect the disposition of the drug substance.

According to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. Caspofungin Accord, 50 mg and 70 mg, powder for concentrate for solution for infusion, contains the same active substance in the same quantity as Cancidas and has the same indications, route of administration, dosage form and posology. Further, it contains the same inactive excipients in similar amounts with the exception of

the buffering agent, where succinic acid has been used instead of glacial acetic acid. This change in the buffering agent is not considered to affect the disposition and the pharmacokinetics of the drug substance as the buffering capacity is suitable to maintain the product pH within the optimum range for caspofungin stability. Hence, CHMP agreed that this difference does not change the suspension on the requirement of performing bioequivalence studies according to Article 10(1) of Directive 2001/83/EC.

Taking into account all aforementioned, not having submitted bioequivalence studies is in line with the above mentioned guideline and considered acceptable by CHMP.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were presented and CHMP agreed that no such studies are required for this application.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and CHMP agreed that no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

According to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

Caspofungin Accord contains the same active substance in the same quantity as Cancidas and has the same indications, route of administration, dosage form and posology. Further, it contains the same inactive excipients in similar amounts, with the exception of the buffering agent where succinic acid has been used instead of glacial acetic acid. This change in buffering agent is not considered to affect the disposition or the pharmacokinetics of the drug substance as the buffering capacity is suitable to maintain the product pH within the optimum range for caspofungin stability.

Taking into account all aforementioned, not having submitted bioequivalence studies is in line with the above mentioned guideline and considered acceptable by CHMP.

The Clinical Overview supports the indications and covers adequately the pharmacology, efficacy and safety of the product.

The proposed SmPC of the Caspofungin Accord is in line with the SmPC of the reference product Cancidas.

2.4.6. Conclusions on clinical aspects

CHMP agreed that Caspofungin Accord 50 mg and 70 mg powder for concentrate for solution for infusion is approvable from a clinical point of view.

2.5. Risk management plan

The CHMP received the following PRAC outcome on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

Important identified risks (s)	Hypersensitivity reactions (including histamine-mediated adverse reactions) Hepatotoxicity 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 or lactation Additional data on the safety and effectiveness in neonates and infants < 3 months of age

Pharmacovigilance plan

No additional pharmacovigilance activities other than routine are requested.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk: Hypersensitivity reactions (including histamine-mediated adverse reactions)	Sections 4.3, 4.4 and 4.8 of Caspofungin Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Hepatotoxicity	Sections 4.4, 4.5 and 4.8 of Caspofungin Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product	None proposed
Important identified risk: Drug resistance	Section 5.1 of Caspofungin Accord SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product	None proposed
Important identified risk: Drug interaction with rifampin and other inducers of drug clearance	Sections 4.2 and 4.5 of Caspofungin Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product	None proposed
Important identified risk: Drug interaction with cyclosporine	Sections 4.4 and 4.5 of Caspofungin Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product	None proposed
Important identified risk:Drug interaction with tacrolimus	Section 4.5 of Caspofungin Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product	None proposed
Missing information: Exposure during Pregnancy or Lactation	Sections 4.6 and 5.3 of Caspofungin Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Additional data on the safety and effectiveness in neonates and infants < 3 months of age	Sections 4.2 and 5.2 of Caspofungin Accord SmPC have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

This application concerns a generic version of caspofungin (as acetate), powder for concentrate for solution for infusion. The reference product Cancidas 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.

No nonclinical studies have been provided for this application, but an adequate summary of the available nonclinical information for the active substance was presented and was considered sufficient by CHMP.

From a clinical perspective, this application does not contain new data on the pharmacokinetics, pharmacodynamics, efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient by CHMP.

CHMP concluded therefore that the benefit-risk balance for Caspofungin Accord is positive.

Having considered both the data submitted in the application and the data available on the chosen reference medicinal product, CHMP is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Caspofungin Accord in the:

- 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.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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 European Medicines Agency;
- 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.