COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Micafungine Pharmazac 50 mg and 100 mg powder for concentrate for solution for infusion (micafungin sodium)

NL/H/5422/001-002/DC

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This module reflects the scientific discussion for the approval of Micafungine Pharmazac 50 mg and 100 mg, powder for concentrate for solution or infusion. The procedure was finalised on 14 July 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 Micafungine Pharmazac 50 mg and 100 mg, powder for concentrate for solution or infusion from Pharmazac S.A.

The product is indicated for:

Adults, adolescents ≥ 16 years of age and elderly:
- Treatment of invasive candidiasis.
- Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.
- Prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / µL) for 10 or more days.

Children (including neonates) and adolescents < 16 years of age:
- Treatment of invasive candidiasis.
- Prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / µL) for 10 or more days.

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 Mycamine (50 mg and 100 mg powder for concentrate for solution for infusion), which has been registered in the EEA by Astellas Pharma Europe B.V., since 25 April 2008 by the centralised procedure EMEA/H/C/000734.

The concerned member states (CMS) involved in this procedure were Cyprus, Greece and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Micafungine Pharmazac 50 and 100 mg, powder for concentrate for solution or infusion is a solid, white to off-white cake and contains as active substance 50 mg or 100 mg of micafungin sodium.

- The 50 mg strength is packed in a 10R Type I amber glass vial closed with a 20 mm bromobutyl rubber stopper and sealed with one piece aluminium seal with a *blue* plastic flip-off cap.
- The 100 mg strength is packed in an 10R Type I amber glass vial closed with a 20 mm bromobutyl rubber stopper and sealed with one piece aluminium seal with a *red* plastic flip-off cap.

The excipients are: lactose monohydrate, citric acid anhydrous (E330) and sodium hydroxide (as solution 0.1%).

II.2 Drug Substance

The active substance is micafungin sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Micafungin is a semisynthetic compound belonging to the new class of antifungal agents, it is an amorphous, hygroscopic white powder and is soluble in water. Micafungin inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls, which is not present in mammalian cells. Micafungin exhibits fungicidal activity against most Candida species and prominently inhibits actively growing hyphae of Aspergillus species. Micafungin sodium exhibits polymorphism, there are three crystal forms (A, B and C) and the amorphous form known. The manufacturer ensures providing the amorphous material consistently.

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 drug substance is produced through three steps. In the first step, an intermediate substrate is produced through fermentation. In the second step the intermediate is transformed by enzyme catalysis, followed by a purification step. After this, a synthesis step is performed to obtain the drug substance micafungin sodium. No ICH class 1 solvents are used in the manufacturing process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

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. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for six pilot scale batches and two full scale batches stored at -20°C ±5°C (36 months) and 5°±3°C (36 months). The batches were stored in polyethylene bags and one aluminium bag contained in suitable drums. Stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. Based on the data submitted, a retest period of 48 months was granted when stored at -20°C ± 5°C.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The main development studies performed were the characterisation of the reference product and the performance of compatibility studies. The development of the product has been described, the choice of excipients is justified and their functions explained. As the test and innovator drug products are to be administered as an infusion and contain the same drug substance in the same quantities as the reference product, no bioequivalence study is required in accordance with the Guideline on the investigation of bioequivalence. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the mixing of micafungin sodium with the excipients and water for injection. This bulk solution is then filtrated aseptically in pre-sterilised vials and lyophilised. A headspace gas is introduce into the vials, after this the vials are stoppered and capped. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur requirements. These specifications are acceptable.

Microbiological attributes

The drug substance is intended to be administered as parenteral drug product. It is aseptically packed and does not contain preservatives. The relevant microbiological tests have been included in the quality control of the product. Furthermore the limits for these tests were established by the MAH and are considered acceptable.

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, water content, reconstitution time, clarity and colour of reconstituted solution, completeness of solution, extractable volume, visual particulate matter and sub-visible particles, pH of reconstituted solution, uniformity of dosage units, identification, assay, related substances, sterility and bacterial

endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life limits are identical, except for the test related substances. The specification is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six full scaled batches from the proposed production site have been submitted, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on six production scaled batches stored at 25°C/60% RH (18 months), 30°C/65% RH (18 months), 30°C/75% RH (18 months) and 40°C/75% RH (6 months). The batches were stored in the proposed packaging. Stability was tested in accordance to the ICH stability guideline. Results remained well within the limits. Photostability studies were performed in accordance with ICH recommendations. The results showed that the product is not stable when exposed to light. As the vial protects the drug product from light, no special storage conditions are required. Based on the results, a shelf life of 30 months can be granted for unopened vials. This medicinal product does not require any special storage conditions.

The in-use stability was assessed and reported as follow:

- *Shelf life reconstituted concentrate in vial* - Chemical and physical in-use stability has been demonstrated for up to 48 hours at 25°C, when reconstituted with sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion.
- *Diluted infusion solution* - Chemical and physical in-use stability has been demonstrated for 96 hours at 25°C when protected from light, when diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion.

Micafungine Pharmazac contains no preservatives. From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use would normally not be longer than 24 hours at 2 to 8°C, unless the reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For the excipient lactose monohydrate, scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Micafungine Pharmazac 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 Micafungine Pharmazac 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.

Due to its nature, micafungin is unlikely to result in a significant risk to the environment, as demonstrated by the predicted environmental concentration in surface water (PEC_{SW}) value of 0.0035 µg/L. Therefore, no ecotoxicological studies were performed with this product. However, an in silico evaluation was performed to provide additional evidence of the environmental safety. The results show that micafungin is not classified as persistent, bioaccumulative and toxic (PBT) or as a very persistent and very bioaccumulative (vPvB) substance. The aquatic ecotoxicity test on the active substance does not show any environmental impact. Additionally, to avoid exposure of the environment aside from excretion from the patients, the specific instructions and precautions for handling and disposal of this product should be followed as directed in section 6.6 of the SmPC.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Mycamine, 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

Micafungine Pharmazac 50 mg and 100 mg, powder for concentrate for solution or infusion 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Micafungine Pharmazac 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.2 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 Micafungine Pharmazac.

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

Important identified risks	• Haemolytic AEs including DIC (disseminated intravascular coagulation) • Hepatic AEs • Renal AEs
Important potential risks	• Relevance in humans of the development of liver tumours in rats • Development of resistant strains
Missing information	• None

It is considered that additional risk minimisation measures are necessary for the safe and effective use of the product. For this, the MAH proposed additional risk minimisation measures (including educational material). These are in line with those of the innovator Mycamine and are therefore accepted. The MAH ensures that prescribers will receive the 'Prescriber Checklist' with the measures prior to prescribing the product, and will evaluate the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation. Besides, the implementation of additional risk minimisation measures based on local authorities requirements will be tracked. The educational material contains the following key elements:

- The decision to use micafungin should take into account a potential risk for the development of liver tumours. Micafungin should therefore only be used if other antifungals are not appropriate.
- Caution must be demonstrated if the patient:
  - has severe liver function impairment
  - has chronic liver diseases known to represent preneoplastic conditions (e.g. advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects)
  - is receiving a concomitant therapy including hepatotoxic and/or genotoxic properties
  - has history of haemolysis, haemolytic anaemia or renal impairment.
- Patients should be carefully monitored for liver damage and for worsening of renal function.
- To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended.
- Patients who develop clinical or laboratory evidence of haemolysis during micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the benefit/risk of continuing micafungin therapy.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Mycamine. As this product is for parental use only, no further bioequivalence studies are required. Therefore, no new clinical studies were conducted. The MAH demonstrated through literature and chemical-pharmaceutical documentation that the proposed product is similar to 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 leaflet (PL) has been performed on the basis of a bridging report making reference to Mycamine (50 mg and 100 mg powder for concentrate for solution for infusion). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Micafungine Pharmazac 50 mg and 100 mg, powder for concentrate for solution or infusion has a proven chemical-pharmaceutical quality and is a generic form of Mycamine (50 mg and 100 mg powder for concentrate for solution for infusion). Mycamine 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 Micafungine Pharmazac with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 July 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