EUROPEAN UNION RISK MANAGEMENT PLAN FOR MYCAMINE (MICAFUNGIN)

Risk Management Plan (RMP) version to be assessed as part of this application	
RMP version number	24.2
Data lock point for this RMP	25 Aug 2025
Date of final sign off	06 Oct 2025
Rationale for submitting an updated RMP	The Mycamine RMP v23.2 has been updated to Sandoz template*.

*Sandoz has acquired Mycamine from Astellas.

Summary of significant changes in this RMP version:

RMP part/module	High level description of major changes
Part I Product overview	Marketing Authorization Holder (MAH) name has been updated from Astellas Pharma Europe BV to Sandoz Pharmaceuticals d.d. Pharmacotherapeutic group, medicinal products to which this RMP refers, invented name(s), marketing authorization procedure, mechanism of action, and dosage have been updated as per the latest summary of product characteristics (SmPC).
Part II - Module SI Epidemiology of the indication(s) and target populations	None.
Part II - Module SII Non-clinical part of the safety specification	None.
Part II - Module SIII Clinical trial exposure	This section has been updated by removing DLP.
Part II - Module SIV Populations not studied in clinical trials	None.
Part II - Module SV Post-authorisation experience	Patient exposure has been updated with the current DLP.
Part II - Module SVI Additional EU requirements for the safety specification	Marketing Authorization Holder (MAH) name has been updated.
Part II - Module SVII Identified and potential risks	Module SVII.3: Search criteria for the presentation of safety concerns has been updated in line with the GVP module V template.
Part II - Module SVIII Summary of the safety concerns	None.

RMP part/module	High level description of major changes
Part III Pharmacovigilance plan (including post-authorisation safety studies)	Study population, Study Objectives and countries data has been updated.
Part IV Plans for post-authorisation efficacy studies	None.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Updated to add the Legal status.
Part VI Summary of the risk management plan	None
Part VII Annexes	Annex 4: MAH name has been updated to Sandoz in TFUQ form. Annex 7: Updated current SmPC details for centralized procedure. Annex 8: Updated table 'Summary of changes to the risk management plan over time'
Other changes	Marketing Authorization Holder (MAH) logo and QPPV details have been updated on the cover page. Cover page title has been updated as per the GVP template. List of table numbers have been updated as applicable.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP	
Version number	Version 23.2
Approved with procedure	Centralized, EMEA/H/C/000734/II/0047
Date of approval (opinion date)	09-Feb-2023

Qualified Person for Pharmacovigilance (QPPV) Details	
QPPV name:	Dr. Mohamed Ali Kotal
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV/deputy.
QPPV/deputy signature:	I am approving this document as Deputy QPPV on behalf of the EU QPPV.

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CLSI	Clinical Laboratory Standards Institute
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CTD	Common Technical Document
d/c	Discontinuation
DIC	Disseminated intravascular coagulation
DLP	Data lock point
EC	Esophageal candidiasis
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	Europe, Middle East and Africa
EPAR	European Public Assessment Report
EU	European Union
EU RMP	European Union Risk Management Plan
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAH	Foci of altered hepatocytes
FDA	Food and Drug Administration
G-PSUR	Global Periodic Safety Update Report
GVP	Good Pharmacovigilance Practice
HA	Health Authority
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplant
IA	Invasive Aspergillosis
IC	Invasive candidiasis
ICU	Intensive Care Unit
INN	Invented name
MAH	Marketing Authorization Holder
MEC	The minimum effective concentration
MIC	Minimum Inhibitory Concentration
NOAEL	No observed adverse effect level

PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person for Pharmacovigilance
SJS	Stevens-Johnson syndrome
SmPC	Summary of product characteristics
TEN	Toxic Epidermal Necrolysis
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WT	Wild type

Part I: Product(s) Overview

Table 1: Part 1.1 Product Overview

Active substance (INN or common name)	Micafungin
Pharmacotherapeutic group (ATC Code)	Antimycotics for systemic use, other antimycotics for systemic use; Anatomical Therapeutic Chemical Classification System ATC code: J02AX05
Marketing Authorization Holder (MAH)	Sandoz Pharmaceuticals d.d
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	Mycamine
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class Micafungin is a water-soluble, semi-synthetic lipopeptide compound, synthesized from a fermentation product of the environmental mould, *Coleophoma empetri*. It is a member of the echinocandin class of antifungal agents.
	Summary of mode of action Micafungin non-competitively inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall. 1,3-β-D-glucan is not present in mammalian cells. Micafungin exhibits fungicidal activity against most Candida species and prominently inhibits actively growing hyphae of Aspergillus species.
	Important information about its composition Micafungin is a water-soluble, semi-synthetic lipopeptide compound, synthesized from a fermentation product of the environmental mould, *Coleophoma empetri*.
Hyperlink to the product information	Current Summary of Product Characteristic and Package leaflet

<table>
<tr><td>Indication(s) in the EEA</td><td>Current:
Mycamine is indicated for:
<u>Adults, adolescents ≥ 16 years of age and elderly:</u>
• 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.
The decision to use Mycamine should take into account a potential risk for the development of liver tumours. Mycamine should therefore only be used if other antifungals are not appropriate.</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
The dose regimen of micafungin depends on the body weight of the patient as given in the following tablets:
<u>Use in adults, adolescents ≥ 16 years of age and elderly</u>
<table>
<tr><td><u>Indication</u></td><td colspan="2"></td></tr>
<tr><td></td><td>Body weight > 40 kg</td><td>Body weight ≤ 40 kg</td></tr>
<tr><td>Treatment of invasive candidiasis</td><td>100 mg/day*</td><td>2 mg/kg/day*</td></tr>
<tr><td>Treatment of oesophageal candidiasis</td><td>150 mg/day</td><td>3 mg/kg/day</td></tr>
<tr><td>Prophylaxis of Candida infection</td><td>50 mg/day</td><td>1 mg/kg/day</td></tr>
</table>
*If the patient's response is inadequate, e.g., persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients ≤ 40 kg.

<u>Treatment duration</u>
<u>Invasive candidiasis:</u> The treatment duration of Candida infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.</td></tr>
</table>

Oesophageal candidiasis: For the treatment of oesophageal candidiasis, Mycamine should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of *Candida* infections: For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery.

Use in children ≥ 4 months of age up to adolescents < 16 years of age

Indication		
	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

*If the patient's response is inadequate, e.g., persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.

Use in children (including neonates) < 4 months of age

Indication	
Treatment of invasive candidiasis	4-10 mg/kg/day*
Prophylaxis of *Candida* infection	2 mg/kg/day

*Micafungin dosed at 4 mg/kg in children less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. If central nervous system (CNS) infection is suspected, a higher dosage (e.g., 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS.

The safety and efficacy in children (including neonates) less than 4 months of age of doses of 4 and 10 mg/kg for the treatment of invasive candidiasis with CNS involvement has not been adequately established in controlled clinical studies.

Treatment duration

Invasive candidiasis: The treatment duration of Candida infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.

Prophylaxis of *Candida* infections:

Micafungin should be administered for at least one week after neutrophil recovery. Experience with Mycamine in patients less than 2 years of age is limited.

Method of administration: For intravenous use.

	For more detailed information on hepatic, renal impairment, paediatric population and method of administration, please refer to approved summary of product characteristics (SmPC).
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for infusion, 50 mg and 100 mg.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indications and target populations

Indication

Invasive candidiasis/candidemia

Incidence:

Candidemia remains the most frequent life-threatening fungal disease [Tortorano et al., 2006]. Incidences may differ substantially between regions and may also vary between institutions within the same geographical locations. Incidences estimated from community- based studies range from 1.4 to 10.4 per 100,000 inhabitant years in Europe [Quindós, 2014]. Incidences estimated from patients-based studies range from 0.6 to 22.0 per 10,000 patient days [Weinberger et al., 2005; Macphail et al., 2002]. Invasive candidiasis (IC) is a problem of increasing relevance in the healthcare setting and, in particular, the Intensive Care Unit (ICU). Intensive Care Units (ICUs) are known to have a ten-fold higher incidence of IC than medical or surgical wards [Ostrosky-Zeichner & Pappas, 2006].

Prevalence:

The prevalence of candidemia was reported to be around 4.5/10,000 hospital discharges [Macphail et al., 2002] and 6.9/100 patients in intensive care units [Kett et al., 2011].

Demographics of the population in the invasive candidiasis/candidemia indication and risk factors for the disease:

The profile of the target population is determined by the risk factors for candidemia which include previous antibiotic exposure, presence of cancer, severe gastrointestinal dysfunction, renal impairment, prolonged administration of steroid therapy, status of post-operations (e.g., transplantation, endotracheal intubation and intravascular catheters) and, most importantly, a stay on the ICU and total parenteral nutrition [Amrutkar et al., 2006].

Main existing treatment options:

Main treatment options include caspofungin, anidulafungin, fluconazole, and amphotericin B [O'Leary et al., 2018]. Other treatment options include flucytosine, isavuconazole, itraconazole, posaconazole, and voriconazole [O'Leary et al., 2018].

Natural history of the indicated condition in the invasive candidiasis/candidemia population, including mortality.

Candida species are reported to be the third most common cause of nosocomial bloodstream infections [Lipsett, 2006]. Several less common Candida species may be emerging, some of which can exhibit resistance to triazoles and/or amphotericin B [Pfaller & Diekema, 2007].

The attributable mortality rate of candidaemia is estimated to be >30%, with a crude mortality rate of >50% [Quindós, 2014]. Improved prophylactic therapeutic strategies are necessary in order to reduce IC-associated mortality [Pfaller & Diekema, 2007].

Important co-morbidities:

Diverse morbidity (e.g., cancer, organ transplant, immunosuppression, sepsis, severe gastrointestinal dysfunction, acute renal failure [ARF], neutropenia) [Amrutkar et al., 2006].

Esophageal Candidiasis

Incidence:

Incidence data for esophageal candidiasis (EC) are very limited, particular for non-human immunodeficiency virus (HIV) infected patients. A 2010 United States (US) study of HIV cohorts from 1994-2007 reported a rate of 5.2 per 1000 person-years for EC [Buchacz et al., 2010]. According to Vazquez, EC occurs in 10-15% of acquired immune deficiency syndrome (AIDS) patients at some point in their lives [Vazquez, 2010].

Prevalence:

About 12% of randomly selected chronic obstructive pulmonary disease (COPD) and 25% randomly selected non-COPD patients had *Candida albicans* in the esophagus [Andersen et al., 1992].

Demographics of the population in the esophageal candidiasis indication and risk factors for the disease:

Several patient groups are at risk of developing EC, including HIV-infected patients, cancer patients, transplant patients and hospitalized patients on antibiotics, steroids or omeprazole [Martínez et al., 2000; Cha & Sobel, 2004]. EC is the most common AIDS-defining opportunistic infection in HIV-infected patients. The widespread use of highly active antiretroviral therapies (HAART) in developed countries has reduced the use of antifungal agents for EC and EC prophylaxis. However, patients who do not adequately respond to HAART continue to have a high risk of developing EC. The recurrence rate of EC is high (up to 90%), with long infection-free period depending on the success of therapeutic restoration of T-cell function [Laine, 1994; Sobel, 2002]

Main existing treatment options:

Fluconazole is indicated to treat oropharyngeal and EC; other treatment options include itraconazole, anidulafungin and caspofungin [Lortholary et al., 2012].

Natural history of the indicated condition in the esophageal candidiasis population, including mortality and morbidity:

Robust mortality rates are not available.

Important co-morbidities:

Diverse morbidity (e.g., cancer, organ transplant, immunosuppression especially AIDS) [Martínez et al., 2000; Cha & Sobel, 2004].

Antifungal Prophylaxis

Incidence:

The most common breakthrough infections in this high-risk target population are invasive aspergillosis (IA) and IC. The incidence of invasive fungal infections varies among patients with hematologic malignancies. The overall incidence rate of 10% is typically reported in acute leukemia patients and 10–20% among allogeneic hematopoietic stem cell transplant (HSCT) recipients [O'Brien et al., 2003]. In recent years, the incidence of invasive infection due to Candida albicans has become less common owing to the widespread prophylactic use of azole antifungal agents but the incidence of IA continues to increase [Maertens, 2007].

Prevalence:

Robust studies on the prevalence of *Candida* infection in patients undergoing allogeneic (HSCT) or patients who are expected to have neutropenia have not been identified.

Demographics of the population in the antifungal prophylaxis indication and risk factors for the disease:

The demographic profile of the target population is determined by the demography of patients receiving HSCT, particularly allogeneic HSCT and the demography of patients suffering from leukemia, particularly acute myeloid leukemia [Pagano et al., 2006; Bhatti et al., 2006].

In most cases, the development of invasive fungal infections is not predictable. For these reasons, antifungal prophylaxis is almost universally used in clinical practice for patients at high risk of invasive fungal infection at defined times, such as post-HSCT and during induction chemotherapy for leukemia patients.

Main existing treatment options:

Fluconazole is indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy. Other treatment options include amphotericin B, itraconazole, voriconazole, posaconazole, and caspofungin [Ko et al., 2017; Cornely et al., 2011].

Natural history of the indicated condition in the antifungal prophylaxis population, including mortality and morbidity:

Invasive fungal infection in HSCT and profoundly neutropenic patients is often fatal, and oropharyngeal candidiasis, EC and mucositis in these patients are associated with reduced food intake and increased morbidity during the very difficult hospital stay. Reported mortality rates of invasive fungal infection typically vary between 18.9% and 80% within at- risk patient populations in hospitals [Pal, 2017; Quindós, 2014; Vandewoude et al., 2004].

Invasive aspergillosis is an uncommon complication of HSCT and solid organ transplant patients and continues to be associated with poor outcome [Morgan et al., 2005]. However, overall mortality attributable to IA has declined to approximately 40% [Pfaller & Diekema, 2007; Pagano et al., 2006].

Important co-morbidities:

Diverse morbidity (e.g., cancer, organ transplant, immunosuppression, neutropenia).

Part II: Module SII - Non-clinical part of the safety specification

The toxicological profile of micafungin was evaluated in safety pharmacology studies, single-dose and repeat dose toxicity studies, genotoxicity studies, reproductive toxicity studies, local tolerance and antigenicity studies as well as toxicity studies with photo-degradated micafungin drug product. In order to assess the relevance and reversibility of foci of altered hepatocytes (FAH) observed in rats, repeated dose studies of 3 to 6 months duration with recovery periods of up to 18-20 months (lifetime assessment) were conducted.

Repeat dose toxicity studies were also conducted in juvenile rats and dogs. Overall, the conducted studies are considered to have adequately assessed the nonclinical safety profile of micafungin.

The following safety concerns identified from nonclinical studies were considered relevant for human use.

Table 2: SII.1: Important Identified, Important Potential Risks and Missing Information from Non-Clinical Data

Safety Concerns	
Important identified risks (confirmed by clinical data) effects	Hemolysis
	Hepatotoxicity
	Urinary tract changes/Renal adverse events
Important potential risks (not refuted by clinical data or which are of unknown significance)	Liver tumor development in rats

Safety concerns identified based on non-clinical data which are no longer relevant and/or have not been confirmed have been removed from the list of safety concerns. The detailed justification has been provided in Part II Module SVII.2.

An outline of the toxicity and safety pharmacology studies with findings relevant to human usage is provided in the table below.

Table 3: SII.2: Toxicity and safety pharmacology studies with findings relevant to human usage

Key safety findings from nonclinical studies (from nonclinical studies)	Relevance to human usage
Reproductive/developmental toxicity	
Rat: reduced pup weight at high doses (32 mg/kg/day); micafungin crossed the placenta and was excreted into milk. Rabbit: one abortion occurred at a high dose (32 mg/kg/day).	There are limited data from the use of micafungin in pregnant women and the potential risk for humans remains largely unknown. It is unknown whether micafungin is excreted in human breast milk. Micafungin should be used during pregnancy only if the benefit outweighs the potential risks and caution should be exercised when micafungin is administered to a nursing woman. Use during pregnancy and lactation has been addressed in the Summary of Product Characteristics (SmPC).
Genotoxicity	
Micafungin was not mutagenic or clastogenic when evaluated in a standard battery of in vitro and in vivo tests, including an in vitro study on unscheduled Deoxyribonucleic acid (DNA) synthesis using rat hepatocytes.	Not applicable
Carcinogenicity	
Rat: development of FAH and hepatocellular tumors were observed. More details are provided below under "Liver tumor development". Dog: no proliferative lesions in the liver.	See "liver tumor development".
Repeat-dose toxicity	
The target organs for micafungin have been detected in repeated dose toxicity studies. In the rat, blood, liver and urinary tract were identified as target organs/sites of micafungin. The liver and the male genital tract were affected in dogs. The exposure levels at which these effects did not occur. No observed adverse effect level (NOAEL) were in the same range as the clinical exposure or lower. The target organs of micafungin for juvenile rats were the same as those identified for adult rats, namely, the blood, liver, and urinary tract. In the juvenile dog, the liver was identified as a target organ, whereas in the adult dog both the liver and male genital tract were affected. The results of these studies are summarized below.	The relevance to human beings is provided below for each of the target organs/sites.
Histamine release	

Rat: dose-dependent histamine release accompanied by an increase in heart rate and a decrease in blood pressure. Dog: increased plasma histamine at doses of 100 mg/kg. Cardiovascular effects not observed.	Allergic-like reactions, most probably due to histamine release, have been reported in humans. The majority were mild to moderate in intensity. Serious reactions such as anaphylaxis and anaphylactoid reactions (including shock) were uncommon and have been addressed in the SmPC.
Hemolysis	
Rat: dose- and duration-dependent hemolytic anemia. Dog: hemolytic anemia not observed. Rabbit: In vitro micafungin had a significant hemolytic effect in rabbit blood at concentrations ≥ 500 µg/mL.	Cases of hemolysis (refer to Section SVII.3) including acute intravascular hemolysis or hemolytic anemia have been reported in patients treated with micafungin. Patients who develop clinical or laboratory evidence of hemolysis during micafungin therapy should be monitored closely for evidence of worsening of these conditions. Hemolytic adverse events (AEs) have been addressed in the SmPC.
Hepatotoxicity	
Rat: dose- and duration-dependent induction of hepatocellular degeneration accompanied by abnormal liver function parameters. The plasma exposure at the NOAEL was approximately in the same range as encountered during clinical use. Dog: centrilobular hypertrophy of hepatocytes without degenerative changes of hepatocytes at dose of 32 mg/kg/day. Abnormal liver function not observed.	Hepatic AEs have been reported, most of which were mild and reversible and did not require medical intervention. Conjoint increases in alanine aminotransferase (ALT) / aspartate aminotransferase (AST) and bilirubin observed in micafungin-treated pediatric patients were likely due to underlying disease(s) and concurrent medication(s). Patients should be monitored for signs of hepatic impairment. Hepatic AEs have been addressed in the SmPC.
Urinary tract changes/Renal AEs	
Rat: high (32 mg/kg/day) repeat doses in adult rats led to histopathological changes in kidney and urinary bladder (including hyperplasia of transitional cells in the urinary bladder) with changes in urinary electrolytes. Hyperplasia of transitional cells in the urinary bladder occurred with a much lower incidence in a second 26-week study in adult rats. The incidence of this finding decreased and disappeared at recovery periods up to 18 months. Dog: no urinary tract toxicity observed.	Renal AEs have been reported and have been addressed in the SmPC.
Liver tumor development	
Rat: After 13 weeks or longer of daily dosing at a dose of 32 mg/kg/day (known to cause hepatotoxicity in rats), FAH was found to develop in the livers of adult rats, and to persist after a 13- week recovery period. Follow-up studies (20 and 32 mg/kg/day micafungin) to assess the reversibility of FAH over the life span of female rats after cessation of 3- or 6-month treatment periods indicated an increase	Although micafungin was found to be non-genotoxic, FAH and/or hepatocellular tumors developed in rats but only after prolonged exposure to high doses of micafungin. There were no cases of hepatic tumors (including hepatocellular carcinoma (HCC)) after micafungin treatment in the clinical trials. During post-marketing experience, only a very few cases of hepatic tumors have been reported with no reasonable evidence for a causal association between micafungin use and the development of the hepatic tumor. The findings in rats have been addressed in the SmPC.

(relative to control) in the number of hepatocellular adenomas found in the 32 mg/kg/day group at the end of the 18- or 20-month recovery periods (4/50 and 8/50 animals after 3- or 6-months of dosing, respectively).	
Key safety findings from nonclinical studies (from nonclinical studies)	**Relevance to human usage**
Only after 6 months of treatment with micafungin (32 mg/kg/day) and 18 months of recovery, were hepatocellular carcinomas observed (2/50 animals). Rat: 3- or 6-months dosing at 20 or 32 mg/kg was associated with the development of FAH in liver, in addition to the liver toxicity described above. Following an 18- or 20-months post-treatment period, an increase (relative to control) in the number of hepatocellular was adenomas found in the 32 mg/kg/day group (4/50 and 8/50 animals after 3- or 6-months of dosing, respectively). Only after 6 months of treatment with micafungin (32 mg/kg/day) and 18 months of recovery, were hepatocellular carcinomas observed (2/50 animals). Micafungin was completely negative in a battery of genotoxicity tests, indicating that a non-genotoxic mechanism is responsible for liver tumor development in rats. Exposure exaggerations where FAH and/or hepatocellular tumors were seen in the 3- and 6-month rat studies were approximately 4- 8 fold higher than the exposures observed in humans at the maximum recommended adult dose (150 mg/day and AUC_{0-24} 166 mcg·h/mL) and approximately 3 fold higher than steady state exposures at the maximum pediatric recommended dose (10 mg/kg/day and AUC_{0-24} 216 mcg·h/mL). The hepatic injury and sustained regenerative cell proliferation during treatment is the likely trigger for FAH development. The hepatotoxic signal was fully reversed in 4 weeks, whereas FAH could develop into tumors during the 18-20 months recovery period. This is unlike humans, where tumors will only develop in in the presence of chronic hepatic inflammation.	

Both the hepatotoxic effect of micafungin and the development of FAH are dose dependent. However, the duration of the exposure appears the most important factor for the development of FAH and liver tumors in rats. The duration of micafungin dosing that was needed for the induction of foci in rat liver was 3 or 6 months, which substantially exceeds the median duration of micafungin dosing in humans which is 15 days (range, 4-42 days in adults; 12-42 days in children) for invasive candidiasis, 14 days for esophageal candidiasis, and 19 days for prophylaxis. Dog: no proliferative lesions in the liver.	
Key safety findings from nonclinical studies (from nonclinical studies)	**Relevance to human usage**
Effects on male reproductive tract	
Rat: inconsistent findings regarding testicular and epididymal toxicity were identified. Male fertility was not affected. Adult dog: lower testes weight, atrophy of seminiferous tubules and decreased sperm in the epididymides were noted after prolonged treatment (39 weeks) at 10 and 32 mg/kg/day. Vacuolation of the seminiferous epithelium, affecting Sertoli cells, was noted at 32 mg/kg/day. Juvenile dog: In a 39-week juvenile dog study, no treatment-related abnormalities were observed in semen examination or pathological examination of the genital organs.	The potential to affect male fertility in humans is unknown. However, no effects on the male reproductive tract have been reported during clinical trials or post-marketing. The findings in male rats and dogs have been described in the SmPC.

Part II: Module SIII - Clinical trial exposure

Cumulatively, 534 healthy volunteers and 5,894 patients have been enrolled into the micafungin clinical trial programs, of which 4,444 patients have received micafungin.

The overall cumulative subject exposure is provided in Table SIII.1 based upon actual exposure data from completed studies. There are currently no ongoing clinical studies with micafungin.

Table 4: SIII.1: Subject Exposure in Micafungin Clinical Trials†

Treatment	Cumulative Subject Exposure (Number of patients)
Active compound micafungin	4,444
Active comparator fluconazole	876
Active comparator caspofungin	368
Active comparator liposomal amphotericin B	402
Active comparator Itraconazole	147
Placebo	191
Total	**6,428**

†Patients and healthy volunteers from the clinical trial database.

The cumulative exposure to micafungin in completed clinical trials by age, gender and ethnic origin is shown in Table SIII.2 and Table SIII.3.

There has been limited experience among females of childbearing potential, in line with the exclusion criteria for the clinical studies.

Table 5: SIII.2: Cumulative Subject Exposure to Micafungin in Clinical Trials† by Age and Gender for active compound Micafungin

Age Range	Number of Subjects		
	Male	Female	Total
Unknown	1	0	1
Neonates (< 1 month)	21	25	46
Infants (1 month to < 2 years)	53	37	90
Children (2 years to < 12 years)	134	114	248
Adolescents (12 years to < 16 years)	50	42	92
Adults (16 years to < 30 years)	516	291	807
Adults (30 years to < 50 years)	1,013	683	1,696
Adults (50 years to < 65 years)	554	338	892
Elderly (≥ 65 years)	355	217	572
Total	**2,697**	**1,747**	**4,444**

†Patients and healthy volunteers from clinical trial database. Missing age information of one patient from ACN-MA-MYC-2013 could not be retrieved but should be at least 18 years based on inclusion criteria.

Table 6: SIII.3: Cumulative Subject Exposure to Micafungin in Clinical Trials by Ethnic Origin

Racial Group	Number of Subjects†
Caucasian	2,477
Black	891
Asian	772
Other	303
Unknown	1
Total	**4,444**

†Patients and healthy volunteers from clinical trial database.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Important exclusion criteria in the clinical development program are discussed in Table SIV.1.

Table 7: SIV.1: Important exclusion criteria in the pivotal clinical trials across the development program

Criterion 1	**Patient is pregnant**
Reason for being an exclusion criterion	Exclusion based on definitions due to lack/limitations of data or experience related to the investigational drug and/or comparator.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	To date, there are no indications from the available post-marketing data that the safety profile in pregnant women and their offspring is different. In clinical practice, the prescribing clinician will make a decision on use of micafungin based on the SmPC and clinical judgment.
Criterion 2	**Patient is lactating**
Reason for being an exclusion criterion	Exclusion based on definitions due to lack/limitations of data or experience related to the investigational drug and/or comparator.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	To date, there are no indications from the available post-marketing data that the safety profile in lactating women and their breastfed infants is different. In clinical practice, the prescribing clinician will make a decision on use of micafungin based on the SmPC and clinical judgment.
Criterion 3	**Patients with hepatic impairment**
Reason for being an exclusion criterion	Exclusion based on definitions due to lack/limitations of data or experience related to the investigational drug and/or comparator.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	There are currently insufficient data available for the use of Mycamine in patients with severe hepatic impairment and its use is not recommended in these patients (Section 4.4 and 5.2 SmPC). In most clinical studies, patients with severe liver impairment were excluded. Criteria for evidence of severe liver disease were defined by: I AST or ALT > 10 times the upper limit of normal (ULN); II Total bilirubin > 5 times ULN.
Criterion 4	**Patients with a concomitant medical condition, whose participation, in the opinion of the investigator and/or medical adviser, may create an unacceptable additional risk.**
Reason for being an exclusion criterion	Exclusions based on definitions concerning general aspects for the conduct of clinical studies according to good clinical practice.

Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In clinical practice, the prescribing clinician will make a decision on use of micafungin based on the SmPC and clinical judgment and hence no supplementary measures are deemed to be necessary.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program for micafungin is unlikely to detect certain types of adverse reactions such as the risk for hepatotoxicity and subsequent potential liver tumor development in patients with severe hepatic impairment. Section 4.2 of the SmPC describes how there are currently insufficient data available for the use of micafungin in patients with severe hepatic impairment, that its use is not recommended in these patients and that treatment should be conducted after careful assessment of the risk/benefit.

The content of Section 4.4 emphasizes the preclinical findings in rats. Section 4.4 also describes how patients should be carefully monitored for liver damage and in the presence of significant and persistent elevation of ALT/AST early discontinuation of treatment is recommended.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

There were no limitations with respect to underlying conditions, race or age categories for IC, and prophylaxis (exceptions outlined below).

Within the EC population, mainly HIV positive patients aged 16 years and older have been studied. Adults and children undergoing an allogeneic or autologous HSCT were studied for prophylaxis to allow conclusive evaluation within a homogenous group at high risk for developing invasive fungal infections. It is recognized that other populations, such as patients with acute leukemia or liver transplant recipients may also benefit with respect to antifungal prophylaxis but such groups have not been studied [Eggimann et al, 2003; Verma et al, 2005].

In most clinical studies, patients with severe liver impairment were excluded. Criteria for evidence of severe liver disease were defined by:

- AST or ALT > 10 times the ULN;
- Total bilirubin > 5 times ULN.

In addition, no clinical data are available at present concerning the use of micafungin in pregnant or lactating woman, since such patients were excluded from clinical studies.

There is some variation in the clinical trial entry criteria, depending on the phase of development but in general, the entry criteria for the phase III multiple dose efficacy and safety studies reflect the population likely to be exposed during the intended and expected use of the product in medical

practice. However, as with most developmental drugs, there may be some differences between the study population and expected use in the market place.

It is envisaged that extrinsic factors will be similar for the study populations and market place patients. Micafungin use will be confined to specialist environments (e.g., intensive transplant units / ICUs). Drug prescribing and administration in such settings is highly regulated and protocol-orientated. The Marketing Authorization Holder therefore believes that prescribing within this framework itself positively shifts the benefit-risk balance to the drug.

The MAH believes that the entry criteria of the pivotal phase III trials reflect the population likely to be exposed during the intended and expected use of micafungin in medical practice. There were no inclusion/exclusion criteria based on age or on conditions more prevalent in a given age group. Nevertheless, one cannot exclude that due to some degree of selection bias from the investigators minimizing the exposure of new compounds to elderly patients, the elderly population included in the clinical trials might be slightly underestimated; however, the safety profile of adults and elderly is similar.

Table 8: SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities:	
1. Patients with hepatic impairment	Patients with severe hepatic impairment were excluded from the clinical trials. Criteria for evidence of severe liver disease were defined by: AST or ALT > 10 times the ULN; Total bilirubin > 5 times ULN.
2. Patients with renal impairment	Excluded due to the comparator agents used in the clinical trials.
3. Patients with cardiovascular impairment	Not applicable.
4. Immunocompromised patients	Within the EC population, mainly HIV positive patients aged 16 years and older have been studied. Adults and children undergoing an allogeneic or autologous HSCT were studied for prophylaxis to allow conclusive evaluation within a homogenous group at high risk for developing invasive fungal infections. Patients with acute leukemia or liver transplant recipients may also benefit with respect to antifungal prophylaxis but such groups have not been studied.
5. Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.

Population with relevant different ethnic origin	There were no limitations with respect to race.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

Market exposure has been calculated using data from available sales volume and assumes that an average daily dose was 99 mg and the average therapy duration was 14.3 days, based on data from post-marketing surveillance in Japan. Patient exposure was calculated using the following formula:

Patients = Gram sold (g) / [Average daily dose (0.099 g)] / 14.3 days.

SV.1.2 Exposure

Table SV.1 shows the cumulative exposure as obtained from sales data. It is estimated that the worldwide cumulative exposure of Mycamine is 3,395,017 patients (Astellas sales till Sep 2024 is estimated to be 3,350,722 patients since the first launch for Astellas[1] and 44,295 patients for Sandoz[2] from 01 Mar 2024 to 31 Jul 2025).

Table 9: SV.1: Estimated Cumulative exposure from Marketing Experience

Marketing Authorization Holder	Period***	Japan Area	United states (US) Area	EEA*	ROW**	Total
Astellas	09 Oct 2002 - till Sep 2024	1,632,909	1,371,285	346,528	NA	3,350,722
Sandoz	01 Mar 2024 - 31 Jul 2025	NA	NA	8,871	35,425	44,295
Total		1,632,909	1,371,285	355,399	35,425	3,395,017

Japan Area: Japan and Asia; US Area: North, Central and South America; EEA: European Economic Area (*including Russia, Switzerland and The Middle East and North Africa / Sub-Saharan African Countries)
ROW**: Rest of the World (Australia, Brazil, Hong Kong, Israel, Malaysia, Singapore, Taiwan, Thailand and Vietnam)
***The Mycamine marketing authorizations were transferred to Sandoz during 2024.

[1] Sandoz EU PBRER for the reporting period: 09-Oct-2022 to 08-Oct-2024
[2] Sandoz has sales for Mycamine from Mar-2024 onwards and included in calculation of patient exposure.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Abuse is unlikely because micafungin is administered as an IV infusion and has neither psycho stimulating effects nor any other effects that might lead to dependency.

Potential for off-label use

Sandoz states that the product is only indicated for the treatment of specific Candida infections (candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses infections), EC, and prophylaxis of Candida infections in patients undergoing HSCT. However, as with many anti-infective agents, off-label use may occur in clinical practice. Micafungin may be used in the treatment of other fungal infections if no effective alternative is available.

To avoid or minimize the potential for off-label use, Sandoz clearly indicates the correct use in the product information for experts Section 4.1 ‘Therapeutic indication’ of SmPC.

Potential for medication error

Micafungin is available as 50 mg and 100 mg single-use vials, coated with a light protective film. To minimize the risk that doses are mistaken, the color of the flip-off cap covers differs for the two doses: blue for 50 mg vials and red for 100 mg vials. The MAH clearly indicates correct use in Section 4.2 and 6.6 of the SmPC. Therefore, it is considered that the description allows simple handling for the correct use of micafungin. Since parenteral medications are prescribed by physicians and administered by trained healthcare professionals (HCPs) in the hospital, the risk for potential medication error is low.

To date, the number of reports of medication errors has been low. The MAH has determined that the micafungin medication errors are not systematic in nature and do not highlight any deficiencies in product labeling. These errors, as documented, do not represent a new safety signal (or product misuse) and do not alter the benefit-risk profile for micafungin.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Module SVII.1 is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Considering the guidance provided in GVP Module V Revision 2, the MAH proposes to remove the following safety concerns from the EU RMP as Important identified risks:

- **Allergic-like/possible histamine-mediated AEs** – This is a well-known risk which has been fully characterized. Therefore, no further evaluation, other than routine pharmacovigilance is considered necessary to investigate this identified risk. It is unlikely that the product will be used in an out-of-hospital setting (Intravenous administration). Risk minimization measures as described in the product information (i.e., contraindication in SmPC Section 4.3 regarding known hypersensitivity with micafungin or other echinocandins and warning in Section 4.4 regarding micafungin withdrawal upon onset of anaphylactic/anaphylactoid reactions) are part of standard clinical practice within the EU. Consequently, the MAH propose to retire the Follow up questionnaire for this risk.

  As this risk is well known to HCPs as also shown by the effectiveness checks during the surveys and considered to be appropriately managed, this risk is expected to have a minimal impact on the risk-benefit balance of the product, also considering the severity of the conditions treated with this product.

- **Stevens-Johnson syndrome and toxic epidermal necrolysis** – Risk is already well-known to HCPs as shown by the effectiveness checks during the surveys. Severe cutaneous adverse reactions have also been observed with other antifungal drugs and are labeled for caspofungin, which is a drug of the same class (echinocandin), therefore the risk is not considered specific to micafungin. Events of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred with a very low frequency based on post-marketing experience. No new safety information (no increase in severity or frequency of events) pertaining to this risk emerged from the collected post-marketing data. Given the low frequency of occurrence of this risk and considering the serious or life-threatening infectious conditions that micafungin intends to treat, this risk is expected to have a minimal impact on the risk-benefit balance of the product.

- **Disseminated intravascular coagulation (DIC)** – Considering that intravascular hemolysis has been suggested as a plausible mechanism for this adverse reaction, this risk has been included as part of “Hemolytic AEs” (a thrombotic microangiopathic

hemolytic anemia) and therefore it has been removed as a separate safety concern and included under the risk of Hemolytic AEs which has been updated as "Hemolytic AEs including DIC". This update is in accordance with the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report (EMEA/H/C/000734/II/0038).

- **Hepatic AEs -** Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized). This update is in accordance with the PRAC assessment report (EMEA/H/C/000734/II/0047).

- **Renal AEs -** Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized). This update is in accordance with the PRAC assessment report (EMEA/H/C/000734/II/0047).

Considering the guidance provided in GVP Module V Revision 2, the MAH proposes to remove the following safety concerns from the EU RMP as Important potential risks:

- **Pancytopenia** – In clinical trials, the incidence of serious adverse events of pancytopenia was low among micafungin-treated patients and none of the events led to death. The post- marketing data collected to date do not confirm a drug-induced etiology of pancytopenia reported in association with micafungin use and pancytopenia is considered to be secondary to underlying disease and/or use of concomitant medications. In addition, pancytopenia is not a listed adverse drug reaction (ADR) for the other two drugs of the echinocandin class (i.e., caspofungin and anidulafungin).

- **Effects on the male reproductive tract** – This important potential risk is based on data from micafungin non-clinical studies (revealing testicular toxicity). Collected post- marketing data since 2002 have not revealed any evidence of micafungin induced adverse effects on the male reproductive tract. Neither have any effects on fertility been observed in pre-clinical studies and post-marketing experience for drugs of same class caspofungin and anidulafungin (source: United Kingdom (UK) SmPC). In conclusion, the clinical evidence gathered to date does not confirm the micafungin non-clinical findings.

- **Drug toxicity with concomitant use of amphotericin B deoxycholate, sirolimus, nifedipine and itraconazole** – This important potential risk is based on data from micafungin drug-interaction studies showing (slightly) increased exposure (AUC) of amphotericin B deoxycholate itraconazole, sirolimus and nifedipine in the presence of micafungin (30%, 22%, 21% and 18% respectively). Collected post-marketing data since 2002 have not revealed any reasonable clinical evidence of amphotericin B deoxycholate itraconazole, sirolimus or nifedipine toxicity in combination with micafungin use. It should be noted that appropriate language on these pharmacokinetic drug interactions is provided in Sections 4.4 and 4.5 of the EU SmPC along with the recommendation to monitor for potential drug toxicity when using any of these drugs in combination with micafungin use. However, no clinical manifestations of these known pharmacokinetic drug interactions have been reported or identified to date.

- **Relevance in humans of the development of liver tumors in rats -** Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized). This update is in accordance with the PRAC assessment report (EMEA/H/C/000734/II/0047).

Considering the guidance provided in GVP Module V Revision 2, the MAH proposes to remove the following safety concerns from the EU RMP as missing information:

- **Reproductive and developmental toxicity** – This safety concern is based on data from micafungin non-clinical studies. For the other two echinocandins (caspofungin and anidulafungin) developmental toxicity was also observed during animal studies (source: Section 5.3 of the UK SmPC). However, to date no clinical data have become available that would support the non-clinical findings (source: Section 4.6 of the caspofungin and anidulafungin UK SmPC). Only a limited number of cases have been reported to date where the mother was exposed to micafungin during pregnancy. Analysis of these cases did not reveal an increased risk of adverse effects on the fetus or course and outcome of pregnancy in pregnant women under micafungin treatment. As there are no indications to date that the effects observed in animals have relevance to human usage, the MAH is of the opinion that this missing information can be removed from the list of safety concerns (also considering that there are no additional pharmacovigilance activities in place for this risk).

For all the risks, which have been proposed to be removed from the list of safety concerns in this RMP, the MAH would like to emphasize that it will continue to monitor these risks through routine pharmacovigilance activities including signal detection.

SVII.3 Details of important identified risks, important potential risk, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Hemolytic AEs including Disseminated intravascular coagulation (DIC)

Search Criteria (MedDRA): High-Level Group Terms HLGT-'Haemolyses and related conditions' and Preferred Term (PT) 'Disseminated intravascular coagulation'.

Potential mechanisms:

One possible mechanism could be surfactant activity of micafungin at very high doses, as observed in pre-clinical studies. The mechanism has not been clearly established for DIC; however, intravascular hemolysis has been suggested as a plausible mechanism.

Evidence source(s) and strength of evidence:

The important identified risk of Hemolytic AEs is based on data from micafungin non- clinical and clinical studies and post-marketing experience. The risk of DIC is mainly based on post-marketing data.

See Module SII. Nonclinical part of the safety specification, Common Technical Document (CTD) Module 5.3.5.3 Integrated Summary of Safety, CTD Module 2.7.4 Summary of Clinical Safety, Global periodic safety update reports (G-PSURs) 1-21.

Characterization of the risk:

Hemolytic AEs:

Table 10: SVII.1: Hemolytic AE frequencies from pooled pivotal phase III trials by preferred term in pediatric patients

Patients < 16 yrs-old [1]			
	Micafungin	AmBisome®	Fluconazole
Preferred terms	N=99	N=56	N=48
Adverse events, regardless of causality	3 (3.0)	1 (1.8)	0
Transfusion reaction	3 (3.0)	1 (1.8)	0

[1] Includes patients from Studies 98-0-050 and FG-463-21-08.

Table 11: SVII.2: Hemolytic AE frequencies from pooled pivotal phase III trials by preferred term in adult patients

Patients 16-64 yrs old [1]				
	Micafungin	AmBisome®	Caspofungin	Fluconazole
Preferred terms	N=1,050	N=179	N=129	N=639

Adverse events, regardless of causality	28 (2.7)	0	1 (0.8)	16 (2.5)
Transfusion reaction	23 (2.2)	0	1 (0.8)	14 (2.2)
Hemoglobin urine present	3 (0.3)	0	0	2 (0.3)
Haemolysis	1 (0.1)	0	0	0
Haemolytic anaemia	1 (0.1)	0	0	0

[1] Includes patients from Studies 98-0-050, 03-7-005, 03-0-192, and FG-463-21-08.

Table 12: SVII.3: Hemolytic AE frequencies from pooled pivotal phase III trials by preferred term in elderly patients

Patients ≥ 65 yrs-old[1]				
	Micafungin	**AmBisome®**	**Caspofungin**	**Fluconazole**
Preferred terms	**N=258**	**N=86**	**N=64**	**N=28**
Adverse events, regardless of causality	2 (0.8)	0	1 (1.6)	1 (3.6)
Transfusion reaction	2 (0.8)	0	1 (1.6)	1 (3.6)
Hemoglobin urine present	1 (0.4)	0	0	0

[1] Includes patients from Studies 98-0-050, 03-7-005, 03-0-192, and FG-463-21-08.

Table 13: SVII.4: Case seriousness and outcomes in clinical efficacy and safety studies (n=3,747)[1] by age-group for Hemolytic AEs

	Number of Subjects (Incidence [%] within age group)		
	< 16 yrs-old	**16-64 yrs old**	**≥ 65 yrs-old**
Category	**N=479**	**N=2,848**	**N=420**
Overall, regardless of relationship	10 (2.1)	46 (1.6)	4 (1.0)
Overall, treatment-related	0	5 (0.2)	0
Not recovered, regardless of relationship [2]	0	7 (0.2)	0
Not recovered, treatment-related [2]	0	3 (0.1)	0
Treatment discontinuation (d/c), regardless of relationship	0	1 (0.0)	0
Fatal, regardless of relationship [3]	0	0	0
Fatal, treatment-related	0	0	0
Serious, regardless of relationship	0	4 (0.1)	0
Serious, treatment-related	0	2 (0.1)	0

[1] Includes 520 healthy volunteers.

[2] At last observation.

[3] Fatal (clinical studies) includes all AEs irrespective of causality recorded as primary reason for death.

Review of post-marketing data for this important identified risk was consistent with findings in the clinical trial database. Rare cases of hemolysis including acute intravascular hemolysis or

hemolytic anaemia have been reported in patients treated with micafungin during post- marketing experience. These reactions are listed as Adverse drug reaction (ADRs) in Section 4.8 of the SmPC and a recommendation to monitor patients who develop clinical or laboratory evidence of hemolysis during micafungin treatment is included in Section 4.4 of the SmPC.

Disseminated intravascular coagulation:

Table 14: SVII.5: Disseminated intravascular coagulation frequencies from pooled pivotal phase III trials by preferred term in pediatric patients

	Patients < 16 yrs-old [1]		
	Micafungin	AmBisome®	Fluconazole
	N=99	N=56	N=48
Adverse events, regardless of causality	0	0	0
DIC	0	0	0

[1] Includes patients from Studies 98-0-050 and FG-463-21-08.

Table 15: SVII.6: Disseminated intravascular coagulation frequencies from pooled pivotal phase III trials by preferred term in adult patients

	Patients 16-64yrs-old [1]			
	Micafungin	AmBisome®	Caspofungin	Fluconazole
	N=1,050	N=179	N=129	N=639
Adverse events, regardless of causality	6 (0.6)	2 (1.1)	1 (0.8)	1 (0.2)
DIC	6 (0.6)	2 (1.1)	1 (0.8)	1 (0.2)

[1] Includes patients from Studies 98-0-050, 03-7-005, 03-0-192, and FG-463-21-08.

Table 16: SVII.7: Disseminated intravascular coagulation frequencies from pooled pivotal phase III trials by preferred term in elderly patients

	Patients ≥ 65 yrs-old [1]			
	Micafungin	AmBisome®	Caspofungin	Fluconazole
	N=258	N=86	N=64	N=28
Adverse events, regardless of causality	0	0	0	0
DIC	0	0	0	0

[1] Includes patients from Studies 98-0-050, 03-7-005, 03-0-192, and FG-463-21-08.

Table 17: SVII.8: Case seriousness and outcomes in clinical efficacy and safety studies (n=3,747)[1] by age-group for Disseminated intravascular coagulation

Category	Number of Subjects (Incidence [%] within age group)		
	< 16 yrs-old	16-64yrs-old	≥ 65 yrs-old
	N=479	N=2,848	N=420
Overall, regardless of relationship	2 (0.4)	11 (0.4)	0
Overall, treatment-related	0	0	0
Not recovered, regardless of relationship [2]	1 (0.2)	5 (0.2)	0
Not recovered, treatment-related [2]	0	0	0
Treatment d/c, regardless of relationship	0	1 (0.0)	0

Fatal, regardless of relationship [3]	0	0	0
Fatal, treatment-related	0	0	0
Serious, regardless of relationship	2 (0.4)	8 (0.3)	0
Serious, treatment-related	0	0	0

[1] Includes 520 healthy volunteers.

[2] At last observation.

[3] Fatal (clinical studies) includes all AEs irrespective of causality recorded as primary reason for death.

This important identified risk is based on post-marketing data (no treatment related events have been observed in the clinical trials as shown above). Review of the post-marketing data and other sources revealed that the total body of evidence supported the causal association between micafungin and the development of DIC. It is of note that no data supported the notion that micafungin directly induces DIC, but the data rather indicates that micafungin may lower the threshold for the development of DIC among patients who are readily at high risk. The event of DIC was added to Section 4.8 of the SmPC following the above-mentioned evaluation.

Risk factors and risk groups:

Risk factors

More than 200 causes for hemolysis exist. The patient populations most likely to experience hemolysis are those who are: elderly, receiving known hemolytic concomitant medications; suffering from bacterial infections/septicemia; with glucose 6 phosphate dehydrogenase deficiency; with sickle cell syndrome or malaria; with solid organ or hematological tumor; with cardiac valve dysfunction/prosthesis; receiving blood transfusions and/or suffering from systemic lupus erythematosus [Schick, 2007]. Disseminated intravascular coagulation (DIC) is an acquired disorder that occurs in a wide variety of clinical conditions, including septicemia, trauma (in particular with extensive tissue injury, head injury, and fat embolism), as an obstetric complication, in some vascular disorders, as a reaction to certain toxins, and in some acute immunologic disorders, and in cancer [Levi & Ten Cate, 1999].

Risk groups

No specific risk groups, besides the known risks at the individual level, have been identified within the micafungin treated population for the risk of hemolytic disorders including DIC.

Preventability:

Patients who develop clinical or laboratory evidence of hemolysis during micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin therapy. The identified risk of hemolysis and hemolytic anemia is included in the adverse reactions Section, and monitoring recommendations, are described in the warnings and precautions Section of the SmPC.

There is no suggested preventive measure besides early intervention for the risk of DIC. The identified risk of DIC is included in the adverse reactions Section of the SmPC.

Impact on the risk-benefit balance of the product:

Hemolytic AEs including DIC seen with micafungin are an important identified risk and could have an impact on the risk-benefit balance. However, the routine and additional risk minimization measures put in place are considered to adequately mitigate this risk.

Public health impact:

In clinical studies, treatment-related hemolytic AEs occurred in 5 out of 3,747 subjects. During post-marketing experience, cases of hemolysis, including intravascular hemolysis, have been reported. Intravascular hemolysis may induce ARF which may result in death. However, appropriate treatments (such as plasma exchange) are effective in preventing fatal outcome. Patients who develop clinical or laboratory evidence of hemolysis during micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin therapy.

Disseminated intravascular coagulation is a typical complication in patients with spreading invasive fungal infections. The mortality associated with DIC depends on the underlying medical condition and the intensity of the coagulation disorder. In a large number of clinical studies, the occurrence of DIC was an independent predictor of mortality. In patients with sepsis or severe trauma, the development of DIC roughly doubles the risk of death [Levi & Ten Cate, 1999].

Important Potential Risk: Development of Resistant Strains

Search Criteria (MedDRA): High-Level Terms (HLT) Candida infections, PTs: Condition aggravated, Drug ineffective, Drug resistance, and Multiple-drug resistance.

Potential mechanisms:

Acquired resistance of Candida species to echinocandins is typically mediated via acquisition of point mutations in the fks genes encoding the major subunit of its target enzyme [Pfaller et al 2012].Evidence source(s) and strength of evidence:

This important potential risk is based on data from micafungin non-clinical studies (annual results of the International Antifungal Surveillance program) and post-marketing experience. G-PSURs 1-21.

Characterization of the risk:

The latest report from the International Antifungal Surveillance for Micafungin (2016) reported the following: the activity of micafungin and comparator agents were tested against 1,688 clinical fungal strains collected during 2016 from sterile sites, respiratory tract and bloodstream infections as part of the SENTRY Antifungal Surveillance Program worldwide. The organisms were collected prospectively from 72 medical centers located in North America (31 sites), Europe (26 sites), the Asia-Pacific Region (9 sites) and Latin America (6 sites). These strains were recovered

consecutively from patients with bloodstream infections (974 isolates), from normally sterile body fluids, tissues, abscesses (133 isolates), from respiratory tract specimens (354 isolates) and those collected from non-specified sites (227 isolates). Identification of the organisms was confirmed at JMI Laboratories using methods standard techniques.

Micafungin also displayed a small number (0 for *C. krusei* ATCC 6258 and 11/15; 6.7% instance for *C. parapsilosis* ATCC 22019) of results out of range. All results were within range upon repeat testing.

Among the 1,688 fungal clinical isolates tested, 1,287 (76.2%) were Candida spp., 65 (3.9%) were non-candidal yeasts, including 42 *Cryptococcus neoformans* var. *grubii* (2.5%), 278 (16.5%) were Aspergillus spp., and 58 (3.4%) were other moulds. The distribution of isolates according to the geographical regions is: 46.3% from North America, 37.4% from Europe, 9.5% from Asia-Pacific, and 6.8% from Latin America. All 580 C. albicans isolates tested were susceptible to micafungin (minimum inhibitory concentration [MIC]50/90, 0.015/0.015 µg/mL) at ≤0.06 µg/mL and 100.0% of isolates were also considered susceptible the other echinocandins using the current Clinical and Laboratory Standards Institute (CLSI) breakpoint criteria. All isolates were susceptible to fluconazole, and voriconazole: 98.8% were wild type (WT) to posaconazole.

Among 268 *C. glabrata* isolates tested, 264 (98.5%) were inhibited by micafungin (MIC50/90, 0.015/0.03 µg/mL) at a concentration of ≤0.06 µg/mL (current CLSI breakpoint). Caspofungin (MIC50/90, 0.03/0.06 µg/mL) and anidulafungin (MIC50/90, 0.06/0.12 µg/mL) inhibited 98.9% and 96.6% of these isolates, respectively, at the current CLSI breakpoint for these compounds. Among 8 isolates displaying echinocandin MIC values greater than the Epidemiological Cutoff Values (ECV) screened for the presence of fks Hot-spot (HS) mutations, 6 displayed amino acid alterations. The most common substitutions were fks1 HS1 S629P (2 isolates) and fks2 HS1 S663P (2 isolates). All but 1 of the echinocandin-non- susceptible isolates were from the US and accounted for 4.6% of North American isolates of *C. glabrata*. The remaining non-susceptible isolate was from Turkey. A total of 5.2% of the *C. glabrata* isolates from 2016 were categorized as resistant to fluconazole.

Against 178 *C. parapsilosis* isolates, micafungin (MIC50/90, 1/2 µg/mL), anidulafungin (MIC50/90, 2/2 µg/mL), and caspofungin (MIC50/90, 0.25/0.5 µg/mL) displayed comparable activity. Micafungin inhibited 99.4% and caspofungin inhibited 100.0% of the tested isolates at the current CLSI breakpoint, whereas 8.4% were intermediate to anidulafungin (MIC 4 µg/mL). Fluconazole was active against 93.8% of the *C. parapsilosis* isolates at the current breakpoint criteria by CLSI. None of the *C. parapsilosis* isolates displayed MIC above the ECV for the echinocandins.

Against 99 *C. tropicalis* isolates, micafungin (MIC50/90, 0.03/0.06 µg/mL), anidulafungin (MIC50/90, 0.03/0.06 µg/mL), and caspofungin (MIC50/90, 0.015/0.06 µg/mL) displayed comparable activity. All 3 echinocandins inhibited 93.9% of the tested isolates at the current CLSI breakpoint. Fluconazole and voriconazole inhibited 97.0% of these isolates according to current breakpoint criteria. Among 7 isolates displaying echinocandin MIC values greater than the ECV screened for the presence of fks HS mutations, 6 displayed amino acid alterations. The most common substitution was fks1 HS1 S645P (5 isolates). All but 2 echinocandin-nonsusceptible

isolates were from the US and accounted for 10.4% of North American isolates of *C. tropicalis*. The remaining 2 non-susceptible isolates were from Brazil and New Zealand.

All 41 *C. krusei* isolates were inhibited by micafungin at ≤0.12 µg/mL and all of these isolates were considered susceptible to the echinocandins. All isolates were WT for posaconazole and 90.2% were susceptible to voriconazole.

Among other Candida species, 100.0% of *C. dubliniensis* and *C. lusitaniae* isolates had micafungin, anidulafungin, and caspofungin MIC values considered WT. Two isolates (6.5%) of *C. lusitaniae* were non-WT to fluconazole, posaconazole, and voriconazole. Among 5 C. pelliculosa isolates, 3 were non-WT to micafungin, 2 harbored mutations in fks1 HS1 (both F665L), and 1 possessed a mutation in fks2 HS1 (F665L). All 3 isolates were from a single institution in Croatia.

All *C. neoformans* var. *grubii* isolates displayed WT MIC values for fluconazole and 5 (11.9%) were non-WT to both voriconazole and posaconazole. The activity of the echinocandins was limited against this species.

All *A. fumigatus* isolates (99.5%), except 1, were inhibited by micafungin (The minimum effective concentration (MEC) 50/90, ≤0.008/0.015 µg/mL) and other echinocandins at ≤0.06 µg/mL. These isolates displayed WT MEC results for caspofungin (100.0%) and voriconazole (99.5%). One isolate was non-WT to posaconazole (MEC, 1 µg/mL) and voriconazole (MEC, 2 µg/mL).

All 28 *A. flavus* isolates were inhibited by micafungin (MEC50/90, 0.015/0.03 µg/mL) at ≤0.03 µg/mL, and this compound displayed similar activity to that of caspofungin (MEC50/90, 0.015 /0.015 go/mL) and anidulafungin (MEC50/90, ≤0.008/0.015 µg/mL).

All 33 *A. niger* isolates were inhibited by micafungin (MEC50/90, 0.015/0.03 µg/mL) at ≤0.06 µg/mL, and this compound displayed similar activity to that of caspofungin (MEC50/90, 0.015/0.03 µg/mL) and anidulafungin (MEC50/90, ≤0.008/0.015 µg/mL).

All 15 *A. terreus* isolates were inhibited by micafungin (MEC50/90, ≤0.008/0.015 µg/mL) at ≤0.015 µg/mL, and this compound displayed similar activity to that of caspofungin (MEC50/90, 0.015/0.015 µg/mL) and anidulafungin (MEC50/90, 0.015/0.03 µg/mL).

The MIC/MEC results for micafungin and selected comparators obtained for isolates grouped as other Candida spp., other yeasts, other Aspergillus spp., and other moulds were also tested and no new susceptibility patterns were identified.

The correlation of the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) broth microdilution methodologies for micafungin was determined by testing 138 Candida spp. isolates randomly selected to represent different geographic regions. The essential agreement (EA; ± 2 log2 dilution steps) between the 2 methods for micafungin was 98.6%.

In conclusion, the activity of micafungin has been stable over the years and echinocandin resistance among species other than C. glabrata is still uncommon. Having said that it is notable that both elevated MIC values (resistant or non-WT) and fks mutations were seen in isolates of *C. tropicalis* and *C. pelliculosa*. The presence of fks HS mutations was noted among the *C. glabrata*, *C. tropicalis* and *C. pelliculosa* isolates with higher MIC values.

Isolates displaying MIC results two- to four-fold dilution above the ECV did not carry those alterations.

To date, the post-marketing data are consistent with the results of the International Antifungal Surveillance program.

Risk factors and risk groups:

In general, factors that may contribute to the development of fungal resistance include: previous (prolonged) antifungal exposure, increased use for prophylaxis or empiric therapy, use of sub-therapeutic levels of antifungal drug during treatment, use of invasive vascular devices (e.g., catheters), infection by biofilm forming strains of fungal pathogens which in general demonstrate increased pathogenicity and resistance to the action of antifungals agents.

In a case-control study to evaluate risk factors for fluconazole resistance in patients with *Candida glabrata* bloodstream infection, increased time at risk and previous fluconazole use were reported as significant risk factors for fluconazole resistance [Lee et al, 2009 & 2010].

Preventability:

The risk of developing resistance can be minimized by controlling modifiable risk factors and appropriate use of antifungal agents by adhering to the recommendations in the product information and treatment guidelines on the appropriate use of antifungal agents.

Impact on the risk-benefit balance of the product:

Development of resistant strains is an important potential risk for micafungin and could have an impact on the risk-benefit balance. However, the routine risk minimization measures put in place are considered to adequately mitigate this potential risk.

Public health impact:

Antifungal resistance is associated with elevated MICs, poorer clinical outcomes, and breakthrough infections during antifungal treatment and prophylaxis. [Pfaller et al 2012].

SVII.3.2. Presentation of the missing information

None

Part II: Module SVIII - Summary of the safety concerns

Table 18: SVIII: Summary of Safety concerns

Summary of safety concerns	
Important identified risks	Hemolytic adverse events (AEs) including disseminated intravascular coagulation (DIC)
Important potential risks	Development of resistant strains
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorization safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Table 19: Part III.1: Specific Adverse Event Follow-Up Questionnaires

Description	Purpose	Safety concern(s) addressed
Specific standardized follow- up questionnaires	Better documentation of the clinical course in reported cases to recognize reaction patterns and support the profound causality assessment.	Hemolytic adverse events including Disseminated intravascular coagulation

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

Table 20: Part III.2 Additional Pharmacovigilance Activities

Study short name and title	International antifungal surveillance study
Rationale and study objectives	Rationale: To provide quantification of amount and extent of MIC increases in resistant strains (safety concerns addressed: development of resistant strains). Objectives: To monitor rate and extent of resistant strains.
Study design	In vitro surveillance utilizing clinical samples
Study population	Not applicable (fungal isolates prospectively collected from medical centers from Europe, North America, Latin America and Asia-Pacific regions).
Milestones	Each PSUR in line with applicable regulatory requirements

III.3 Summary Table of additional Pharmacovigilance activities

Table 21: Part III.3: Ongoing and planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None	NA	NA	NA	NA

Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
International antifungal surveillance study Ongoing	To collect strains from clinical sites worldwide and to monitor for resistance based on approved breakpoints.	Development of resistant strains	Annual update	Results are reported on an annual basis.

Part IV Plans for post-authorization efficacy studies

No post-authorization efficacy studies are in place or planned.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 22: Part V.1 Description of Routine Risk Minimization Measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Hemolytic AEs including Disseminated intravascular coagulation	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Routine risk minimization activities recommending specific clinical measures to address the risk:** Specific recommendation for patients who develop clinical or laboratory evidence of haemolysis (including acute intravascular haemolysis or haemolytic anaemia) during micafungin therapy to be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin therapy, is included in SmPC Section 4.4.
Important potential risks	
Development of resistant strains	**Routine risk communication:** SmPC section: 5.1 Legal status: Prescription only
Missing information	
None	

V.2. Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimization measures

Table 23: Part V.3: Summary of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Hemolytic AEs including Disseminated intravascular coagulation	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific standardized follow-up questionnaires **Additional pharmacovigilance activities:** None
Important potential risks		
Development of resistant strains	**Routine risk minimization measures:** SmPC section 5.1 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** International antifungal surveillance study
Missing information		
None		

Part VI: Summary of the risk management plan

Summary of risk management plan for Mycamine (Micafungin)

This is a summary of the risk management plan (RMP) for Mycamine. The RMP details important risks of Mycamine, how these risks can be minimized, and how more information will be obtained about Mycamine's risks and uncertainties (missing information).

Mycamine's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Mycamine should be used.

This summary of the RMP for Mycamine should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Mycamine's RMP.

I. The medicine and what it is used for

Mycamine is authorized 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. (see SmPC for the full indication).

It contains micafungin as the active substance, and it is given by intravenous infusion.

Further information about the evaluation of Mycamine's benefits can be found in Mycamine's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Search | European Medicines Agency (EMA).

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Mycamine, together with measures to minimize such risks and the proposed studies for learning more about Mycamine's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Mycamine are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Mycamine. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hemolytic Adverse events (AEs) including Disseminated intravascular coagulation (DIC)
Important potential risks	Development of resistant strains
Missing information	None

II.B Summary of important risks

Important identified risk: Hemolytic AEs including Disseminated intravascular coagulation	
Evidence for linking the risk to the medicine	This important identified risk is based on data from micafungin non-clinical and clinical studies and post-marketing experience.

Risk factors and risk groups	Risk factors More than 200 causes for hemolysis exist and the patient populations most likely to experience hemolysis are those who are: elderly, receiving known hemolytic concomitant medications, suffering from bacterial infections/septicemia, with glucose 6 phosphate dehydrogenase deficiency, with sickle cell syndrome or malaria, with solid organ or hematological tumor, with cardiac valve dysfunction/prosthesis, receiving blood transfusions and/or suffering from systemic lupus erythematosus [Schick, 2007]. DIC is an acquired disorder that occurs in a wide variety of clinical conditions, including septicemia, trauma (in particular with extensive tissue injury, head injury, and fat embolism), as an obstetric complication, in some vascular disorders, as a reaction to certain toxins, in some acute immunologic disorders, and in cancer [Levi & Ten Cate, 1999]. Risk groups No specific risk groups, besides the known risks at the individual level, have been identified within the micafungin treated population.
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** • None

Important potential risk:	**Development of resistant strains**
Evidence for linking the risk to the medicine	This important potential risk is based on data from micafungin non-clinical studies (annual results of the International Antifungal Surveillance program) and post-marketing experience.
Risk factors and risk groups	In general, factors that may contribute to the development of fungal resistance include: previous (prolonged) antifungal exposure, increased use for prophylaxis or empiric therapy, use of sub-therapeutic levels of antifungal drug during treatment, use of invasive vascular devices (e.g., catheters), infection by biofilm forming strains of fungal pathogens which in general demonstrate increased pathogenicity and resistance to the action of antifungals agents. In a case-control study to evaluate risk factors for fluconazole resistance in patients with *Candida glabrata* bloodstream infection, increased time at risk and previous fluconazole use were reported as significant risk factors for fluconazole resistance [Lee et al, 2009 & 2010].
Risk minimization measures	**Routine risk minimization measures:** • SmPC Section 5.1 Legal status: Prescription only

	Additional risk minimization measures: • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • International antifungal surveillance study See [Section II.C] of this summary for an overview of the post-authorization development plan.

II. C. Post-authorization development plan

II.C.1 Studies which are conditions of the Marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Mycamine.

II.C.2 Other studies in post-authorization development plan

The following category 3 study is an ongoing additional pharmacovigilance activity to address fungal resistance development.

International antifungal surveillance study / program: Ongoing surveillance study of resistant strain development.

Purpose of the study: To collect strains from clinical sites worldwide and to monitor for resistance to micafungin and other antifungal agents based on approved EUCAST breakpoints. The study will provide quantification of amount and extent of MIC increases in resistant strains and the results will be reported on an annual basis.

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Specific Adverse Drug Reaction Follow-up Questionnaires

Follow-up Questionnaire for Hemolytic Adverse Events (this includes DIC for which the questionnaire will also be submitted)

Follow-up Questionnaire for Hemolytic Adverse Events, v.2.0 (including DIC for which the questionnaire will also be submitted)

Case Number:				
Reported Event:		**Patient Details:**	Age/Age group	☐ Male ☐ Female

Thank you for reporting the initial report related to Hemolytic Adverse Event during the use of Mycamine.
With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case.

SIGNS AND SYMPTOMS OF THE EVENT

☐ Anemia	☐ Headache
☐ Jaundice	☐ Hypotension or shock
☐ Hematuria	☐ Palpitation
☐ Petechiae	☐ Nausea
☐ Back pain	☐ Renal insufficiency
☐ Bradycardia	☐ Respiratory symptoms:
☐ Chills	☐ Tachycardia
☐ Fever	☐ Other:

UNDERLYING CONDITIONS / RISK FACTORS

☐ Alcohol use (units per week):	☐ Paroxysmal hemoglobinuria
☐ Blood transfusion	☐ Schistocytes
☐ Bacterial infection / sepsis	☐ Sickle cell syndrome
☐ Cardiac valve dysfunction / prosthesis	☐ Solid organ cancer
☐ Disseminated intravascular coagulation	☐ Splenomegaly
☐ Disturbance of lipid metabolism	☐ Thrombocytopenia
☐ Glucose-6-phosphate dehydrogenase deficiency	☐ Thrombotic thrombocytopenic purpura
☐ Hematological malignancy	☐ Possible drug interaction
☐ Hemolytic uremic syndrome	☐ Smoking (packs per week):
☐ Systemic lupus erythematosus	☐ Other:
☐ Malaria	

MEDICATION

Drug Name	Suspect Product (S) Concomitant (C) AE Treatment (T)	Indication	Dose/Frequency/ Route of Administration	Start Date dd-Mmm-yyyy	Stop Date dd-Mmm-yyyy or Ongoing
☐ Cephalosporin					
☐ Chlorpropamid					
☐ Hydralazin					
☐ L-Dopa					
☐ Nalidixic acid					
☐ Penicillin antibiotics					
☐ Quinidine					
☐ Sulfonamid					
☐					

RELEVANT INVESTIGATIONS Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.		
INVESTIGATION	**DATE** dd-Mmm-yyyy	**RESULT/UNIT**
☐ Bilirubin (specify type):		
☐ Bone marrow/trephine biopsy		
INVESTIGATION	**DATE** dd-Mmm-yyyy	**RESULT/UNIT**
☐ Cold agglutinin titer		
☐ Coombs test direct		
☐ Coombs test indirect		
☐ Haptoglobin (serum)		
☐ Hemoglobin (serum)		

ADDITIONAL DETAILS / OTHER RELEVANT INFORMATION

REPORTER INFORMATION		
REPORTER NAME / CREDENTIALS	**DATE** (dd-Mmm-yyyy)	**SIGNATURE** (to confirm the accuracy of the data)

Annex 6 - Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.