EU RISK MANAGEMENT PLAN

MICAFUNGIN (MYCAMINE™)

The Astellas Group

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EU Risk Management Plan for Mycamine™ (micafungin)

RMP version to be assessed as part of this application:

RMP Version number: 23.2

Data lock point for this RMP: 26-Apr-2022

The data lock point is based on the date of the final approval of NI-PASS (9463-PV-0002) study report which is 26-Apr-2022.

Date of final sign-off: 09-Feb-2023

Rationale for submitting an updated RMP: The results of non-interventional PASS (9463-PV-0002) assessing the effectiveness of the revised Prescriber's Checklist have been evaluated. As a consequence, it has been proposed to retire the Prescriber's Checklist. In addition, final results from the MYCOS post-authorization safety study have been incorporated.

Summary of significant changes in this RMP
Please refer to table below.

Part/Module/Annex	RMP version when section last updated / EMA approval date	Major changes
Part I Product(s) Overview	22.1, 17-Jan-2019	None
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	22.1, 17-Jan-2019	None
SII Non-clinical part of the safety specification	22.1, 17-Jan-2019	None
SIII Clinical trial exposure	22.1, 17-Jan-2019	None
SIV Populations not studied in clinical trials	22.1, 17-Jan-2019	None
SV Post-authorization experience	22.1, 17-Jan-2019	None
SVI Additional EU requirements for the safety specification	22.1, 17-Jan-2019	None
SVII Identified and potential risks	23.2, TBD	Results of MYCOS study (9463-CL-1401) have been incorporated and references to the Prescriber's Checklist have been removed.

		Reclassification of the risks: Hepatic AEs, Renal AEs and Relevance in humans of the development of liver tumors in rats.
SVIII Summary of the safety concerns	23.2, TBD	Removal of the safety concerns Hepatic AEs, Renal AEs and Relevance in humans of the development of liver tumors in rats.
Part III Pharmacovigilance Plan (Including Post Authorization Safety Studies)	23.2, TBD	Two additional pharmacovigilance (PV) activities (MYCOS [Study 9463-CL-1401] and the Effectiveness Check of the Prescriber's Checklist study [NI-PASS 9463-PV-0002]) have been completed*. Both studies have been removed from the PV plan. Removed information related to Hepatic AEs, Renal AEs and Relevance in humans of the development of liver tumors in rats.
Part IV Plan For Post-Authorization Efficacy Studies	22.1, 17-Jan-2019	None
Part V Risk Minimization Measures (Including Evaluation Of The Effectiveness Of Risk Minimization Activities)	23.2, TBD	Description of routine risk minimization measures for the safety concerns Hepatic AEs, Renal AEs and Relevance in humans of the development of liver tumors in rats was removed. Prescriber's Checklist was retired.
Part VI Summary of Risk Management Plan	23.2, TBD	Hepatic AEs, Renal AEs and Relevance in humans of the development of liver tumors in rats were removed from the "List of important risks and missing information" and summary of important risk and potential risk respectively.
Part VII Annexes		
Annex 1 Eudravigilance Interface	22.1, 17-Jan-2019	None
Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study program	23.2, TBD	Two additional PV activities (MYCOS [Study 9463-CL-1401] and Effectiveness Check of the Prescriber's

		Checklist study [NI-PASS 9463-PV-0002]) have been completed*. Tables updated accordingly (including hyperlink to final study reports).
Annex 3 Protocols for proposed, ongoing, and completed studies in the Pharmacovigilance Plan	23.2, TBD	Details updated for MYCOS (Study 9463-CL-1401) and the Effectiveness Check of the Prescriber's Checklist study (NI-PASS 9463-PV-0002) which have both been completed*.
Annex 4 Specific adverse event follow-up forms	23.2, TBD	Updated version 2.0 of the questionnaire has been included.
Annex 5 Protocols for proposed and ongoing studies in RMP Part IV	19.1, 14-Jun-2018	None
Annex 6 Details of proposed additional risk minimization measures (if applicable)	23.2, TBD	Prescriber's checklist is removed due to retirement.
Annex 7 Other supporting data (including referenced material)	22.1, 17-Jan-2019	None
Annex 8 Summary of changes to the risk management plan over time	23.2, TBD	Updated to reflect changes made in this version of the RMP and present procedure numbers and EMA approval dates.

* The MYCOS final study report was submitted to EMA in November 2018. The current RMP update (v 23.2) is consequential to the completion of the NI-PASS 9463-PV-0002 study.

Other RMP versions under evaluation:

RMP Version Number(s)	Submitted on	Procedure Number(s)
There are no RMP versions under review	N/A	N/A

Details of the currently approved RMP:

Version number:	Version 22.1
Approved with procedure:	Centralized, EMEA/H/C/000734/II/0038
Date of approval (opinion date)	17-Jan-2019

QPPV approval/oversight:

QPPV name:	Ralph Nies
QPPV signature:	Electronic signature appended at the end of the document

List of Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
APEL	Astellas Pharma Europe Limited
ARF	Acute renal failure
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from 0 to 24 hours
CIS	Commonwealth of Independent States
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
ECV	Epidemiological Cutoff Values
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EU RMP	European Union Risk Management Plan
FAH	Foci of altered hepatocytes
FDA	Food and Drug Administration
G-PSUR	Global Periodic Safety Update Report
GVP	Good pharmacovigilance practices
HAART	Highly active antiretroviral therapy
HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HS	Hot-spot
HSCT	Hematopoietic stem cell transplant
IA	Invasive Aspergillosis
IC	Invasive Candidiasis

Abbreviation	Definition
ICU	Intensive Care Unit
IMS	International Medical Statistics
JP	Japan
MAH	Marketing Authorization Holder
MEC	Minimum effective concentration
MIC	Minimum inhibitory concentration
NA	Not applicable
NI-PASS	Non-interventional Post-Authorization Safety Study
NOAEL	No observed adverse effect level
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TBD	To be determined
TEN	Toxic epidermal necrolysis
UK	United Kingdom
ULN	Upper limit of normal
US	United States of America
WT	Wild type

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PART I. PRODUCT(S) OVERVIEW

Table Part I.1 Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Micafungin
Pharmacotherapeutic group(s) (ATC Code)	ATC code: J02AX05
Marketing Authorization Holder (MAH)	Astellas Pharma Europe BV
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Mycamine
Marketing authorization procedure	Centralized
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 has been shown to demonstrate highly selective inhibition of the synthesis of 1, 3-β-D-glucan, an essential glucose polymer that provides rigidity and osmotic/structural integrity to the cell wall of susceptible fungi. Chitin or mannan synthesis is not affected and there is no inhibitory activity against the biosynthesis of proteins or nucleic acids. Morphologically, the treatment of *Candida* and *Aspergillus* organisms with micafungin result in thin cell walls, abnormal septum formation, inhibition of germination and hyphal extension, swelling and abnormal extension of hyphal tips with subsequent lysis. Mechanism-based human toxicity with 1, 3-β-D-glucan synthesis inhibitors is unlikely to occur since 1, 3-β-D-glucan is present in fungal cell walls but absent in mammalian cells.
	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*.

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<table>
<tr><td>Hyperlink to the product information</td><td>Module 1.3.1.</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current (if applicable):
Micafungin 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.
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.</td></tr>
<tr><td>Proposed (if applicable):</td></tr>
<tr><td>Dosage in the EEA</td><td>Current (if applicable):
The dose regimen of Mycamine depends on the body weight of the patient as given in the following tables.
Use in adults, adolescents ≥ 16 years of age and elderly
<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.</td></tr>
</table>

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Dosage in the EEA (*continued*)

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.

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 (see Section 5.2).

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.

Proposed (if applicable):

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Pharmaceutical form(s) and strengths	Current (if applicable): Lyophilisate for solution for infusion, 50 mg and 100 mg. White compact lyophilized powder.
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the indication(s) and target population(s)

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). 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).

Module SII. Nonclinical 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 (life time 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 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 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).

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Table 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
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 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 $\geq$ 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 AEs have been addressed in the SmPC.

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Table 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
Hepatotoxicity	
Rat: dose- and duration-dependent induction of hepatocellular degeneration accompanied by abnormal liver function parameters. The plasma exposure at the No Observed Adverse Effect Level (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 (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).	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.

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Table 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
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.	

Table continued on next page

Table 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
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.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours; DNA: deoxyribonucleic acid; FAH: foci of altered hepatocytes; HCC: hepatocellular carcinoma; NOAEL: no-observed adverse effect level; SmPC: summary of product characteristics

Module SIII. Clinical trial exposure

Cumulatively until Data Lock Point (DLP 31 Mar 2018), 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 exposures are provided in Table SIII.1 based upon actual exposure data from completed studies. There are currently no ongoing clinical studies with micafungin.

Table 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 as of DLP, 31-Mar-2018.

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 SIII.2: Cumulative Subject Exposure to Micafungin in Clinical Trials† by Age and Gender

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 as of DLP, 31-Mar-2018. 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 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 as of DLP, 31-Mar-2018.

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 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.**

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

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.

ALT: alanine transaminase; AST: aspartate transaminase; SmPC: summary of product characteristics; ULN: upper limit of normal

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 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.

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

Type of special population	Exposure
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.

ALT: alanine transaminase; AST: aspartate transaminase; EC: esophageal candidiasis; HIV: human immunodeficiency virus; HSCT: hematopoietic stem cell transplant; ULN: upper limit of normal

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 up to 30 Sep 2017 is estimated to be 2,239,045 patients since the first launch.

Table SV.1: Estimated Cumulative exposure from Marketing Experience

PSUR	Period	JP Area	US Area	EEA*	Total
PSUR_1	09 Oct 2002 - 08 Apr 2003	10,888	0	0	10,888
PSUR_2	09 Apr 2003 - 08 Oct 2003	28,503	0	0	28,503
PSUR_3	09 Oct 2003 - 08 Apr 2004	32,413	0	0	32,413
PSUR_4	09 Apr 2004 - 08 Oct 2004	36,346	0	0	36,346
PSUR_5	09 Oct 2004 - 08 Oct 2005	74,782	8,309	0	83,091
PSUR_6	09 Oct 2005 - 08 Oct 2006	69,514	12,267	0	81,781
PSUR_7	09 Oct 2006 - 08 Oct 2007	74,179	18,545	0	92,724
PSUR_8	09 Oct 2007 - 08 Oct 2008	72,327	32,360	38	104,725
PSUR_9	09 Oct 2008 - 08 Apr 2009	36,795	22,991	37	59,823
PSUR_10	09 Apr 2009 - 08 Oct 2009	38,254	30,866	152	69,272
PSUR_11	09 Oct 2009 - 08 Apr 2010	39,701	34,635	1,016	75,352
PSUR_12	09 Apr 2010 - 08 Oct 2010	44,281	38,285	827	83,393
PSUR_13	09 Oct 2010 - 08 Apr 2011	45,769	41,082	1,818	88,669
PSUR_14	09 Apr 2011 - 08 Oct 2011	45,470	34,378	1,995	81,843
PSUR_15	09 Oct 2011 - 08 Apr 2012	46,926	47,641	3,052	97,619
PSUR_16	09 Apr 2012 - 08 Oct 2012	41,790	51,694	5,566	99,050
PSUR_17	09 Oct 2012 - 08 Oct 2013	91,827	104,255	15,013	211,095
PSUR_18	09 Oct 2013 - 08 Oct 2014	103,201	100,219	17,380	220,800
PSUR_19	09 Oct 2014 - 08 Oct 2015	97,767	106,462	19,555	223,78
PSUR_20	09 Oct 2015 - 08 Oct 2016	102,523	105,969	22,777	231,269
PSUR_21	09 Oct 2016 - 08 Oct 2017	103,962	98,559	24,084	226,605
Total		**1,237,218**	**888,517**	**113,310**	**2,239,045**

JP Area: Japan and Asia; US Area: North, Central and South America; EEA: European Economic Area (*including Russia, Switzerland and MENA/SSA); PSUR: periodic safety update report

The table below (Table SV.2) represents the global patient exposure by previous submissions.

To calculate the cumulative market exposure by region and age group, the same age factors applied to the interval period were applied to the cumulative data. This is due to the limited availability of historical patient demographic data.

Regional data was not available for PSUR 1- 7; therefore, the Global data was split based on launch timing. Micafungin launched in Japan in 2002, US in 2005, and Europe in 2007.

Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 8 (09 Oct 2007 - 08 Oct 2008)	JP-area	72,327
	US-area	32,360
	EEA	38
	Total	**104,725**
PSUR 9 (09 Oct 2008 - 08 Apr 2009)	Japan	34,064
	Other Asian Countries	2,731
	US-area	22,991
	EEA	37
	Total	**59,823**
PSUR 10 (09 Apr 2009 - 08 Oct 2009)	Japan	35,354
	Other Asian Countries	2,900
	US-area	30,866
	EEA (Total)	92
	UK	24
	Germany	23
	Slovakia	21
	Finland	9
	Czech Rep.	8
	Sweden	1
	Spain	4
	Denmark	2
	Middle East Countries	60
	Total	**69,272**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 11 (09 Oct 2009 - 08 Apr 2010)	Japan	34,369
	Other Asian Countries	5,332
	US-area	34,635
	EEA (Total)	894
	Germany	208
	Spain	155
	Czech Rep.	112
	Norway	84
	UK	83
	France	62
	Finland	62
	Slovakia	48
	Poland	30
	Hungary	26
	Austria	17
	Italy	4
	Denmark	2
	Sweden	1
	Middle East Countries	122
	Total	**75,352**
PSUR 12 (09 Apr 2010 - 08 Oct 2010)	Japan	37,001
	Other Asian Countries	7,280
	US-area	38,285
	EEA (Total)	739
	Spain	166
	Germany	144
	UK	101
	France	75
	Finland	71
	Czech Rep.	62
	Poland	50
	Slovakia	21
	Austria	19
	Italy	17
	Norway	12
	Hungary	1
	Denmark	0
	Sweden	0
	Middle East Countries	88
	Total	**83,393**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 13 (09 Oct 2010 - 08 Apr 2011)	Japan	38,020
	Other Asian Countries	7,749
	US-area	41,082
	EEA (Total)	1,638
	Spain	362
	Germany	328
	France	208
	Finland	137
	UK	129
	Czech Rep.	108
	Norway	96
	Poland	88
	Hungary	64
	Italy	52
	Austria	40
	Slovakia	26
	Sweden	0
	Middle East Countries	180
	Total	**88,669**
PSUR 14 (09 Apr 2011 - 08 Oct 2011)	Japan	36,871
	Other Asian Countries	8,599
	US-area	34,378
	EEA (Total)	1,715
	Germany	350
	Spain	331
	Finland	188
	UK	185
	France	145
	Norway	113
	Italy	110
	Czech Rep.	92
	Austria	76
	Poland	63
	Hungary	31
	Slovakia	27
	Denmark	4
	Sweden	0
	Middle East Countries	280
	Total	**81,843**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 15 (09 Oct 2011 - 08 Apr 2012)	Japan	37,680
	Other Asian Countries	9,246
	US-area	47,641
	EEA (Total)	2,693
	Germany	527
	Spain	532
	Finland	257
	UK	315
	France	330
	Norway	83
	Italy	202
	Czech Rep.	155
	Austria	69
	Poland	92
	Hungary	69
	Slovakia	42
	Denmark	11
	Sweden	9
	Middle East Countries	359
	Total	**97,619**
PSUR 16 (09 Apr 2012 - 08 Oct 2012)	Japan	39,026
	Other Asian Countries	2,764
	US-area	51,694
	EEA (Total)	5,199
	Germany	659
	Spain	685
	Finland	240
	UK	643
	France	392
	Norway	130
	Italy	456
	Czech	204
	Austria	163
	Poland	176
	Hungary	108
	Slovakia	0
	Denmark	12
	Sweden	28
	Russia	493
	Greece	807
	Iceland	2
	Netherlands	1
	Middle East Countries	367
	Total	**99,050**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 17 (09 Oct 2012 - 08 Oct 2013)	Japan	73,378
	Other Asian Countries	18,450
	US area	104,255
	EEA (Total)	10,803
	German	1,467
	Spain	1,799
	Finland	475
	UK	1,049
	France	858
	Norway	316
	Italy	1,242
	Czech	406
	Austria	316
	Poland	490
	Hungary	164
	Denmark	50
	Sweden	148
	Greece	1,870
	Iceland	3
	Netherlands	95
	Portugal	7
	Romania	5
	Slovenia	43
	Switzerland	3
	APEL Trading	1,543
	Russia/Ukraine/CIS	1,308
	MENA/SSA	1,359
	Total	**211,095**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 18 (09 Oct 2013 - 08 Oct 2014)	Japan	72,452
	Other Asian Countries	30,749
	US area	100,219
	EEA (Total)	13,732
	Germany	1,685
	Spain	2,085
	Finland	243
	UK	1,439
	France	1,375
	Norway	473
	Italy	1,750
	Czech	502
	Austria	418
	Poland	660
	Hungary	241
	Denmark	3
	Sweden	310
	Greece	2,078
	Iceland	16
	Netherlands	146
	Portugal	168
	Romania	28
	Slovenia	112
	Switzerland	14
	APEL Trading	918
	Russia/Ukraine/CIS	1,430
	MENA/SSA	1,286
	Total	**220,800**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 19 (09 Oct 2014 - 08 Oct 2015)	Japan	72,154
	Other countries in Asia and Oceania	25,613
	US area	106,462
	EEA (Total)	16,489
	Germany	1,825
	Spain	2,419
	Finland	52
	UK	1,895
	France	1,649
	Norway	461
	Italy	2,401
	Czech	573
	Austria	612
	Poland	809
	Hungary	214
	Denmark	3
	Sweden	388
	Greece	2,331
	Iceland	10
	Netherlands	323
	Portugal	212
	Romania	97
	Slovenia	215
	Slovakia	0
	Cyprus	0
	Croatia	0
	Lithuania	0
	Latvia	0
	Estonia	0
	Switzerland	4
	Russia	2,030
	MENA/SSA	1,032
	Total	**223,784**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 20 (09 Oct 2015 – 08 Oct 2016)	Japan	67,629
	Other countries in Asia and Oceania†	34,894
	US area	105,969
	EEA (Total)	18,503
	Germany	2,144
	Spain	2,643
	Finland	121
	UK	1,877
	France	1,719
	Norway	325
	Italy	2,678
	Czech	644
	Austria	782
	Poland	908
	Hungary	150
	Denmark	3
	Sweden	728
	Greece	2,373
	Iceland	23
	Netherlands	432
	Portugal	392
	Romania	83
	Slovenia	250
	Slovakia	46
	Cyprus	24
	Croatia	91
	Lithuania	0
	Latvia	0
	Estonia	67
	Switzerland	8
	Russia	2,055
	MENA/SSA	2,211
	Total	**231,269**

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Table SV.2: Post-marketing Exposure broken down by region

PSUR (Period)	Region	Patients
PSUR 21 (09 Oct 2016 - 08 Oct 2017)	Japan	66,398
	Other countries in Asia and Oceania	37,564
	US area	98,559
	EEA (Total)	20,335
	Germany	2,252
	Spain	2,857
	Finland	376
	UK	1,991
	France	1,929
	Norway	371
	Italy	3,209
	Czech	680
	Austria	909
	Poland	1,035
	Hungary	90
	Denmark	0
	Sweden	754
	Greece	2,476
	Iceland	43
	Netherlands	413
	Portugal	400
	Romania	144
	Slovenia	190
	Slovakia	41
	Cyprus	0
	Croatia	130
	Lithuania	0
	Latvia	0
	Estonia	45
	Switzerland	13
	Russia	1,819
	MENA/SSA	1,917
	Total	**226,605**
PSUR 1 to PSUR 21	**Cumulative total**	**2,239,045**

US: United States; EEA: European Economic Area; UK: United Kingdom; CIS: Commonwealth of Independent States; PSUR: periodic safety update report
APEL Trading: Astellas Pharma Europe Limited, Refers to sales to Partner in Middle East
MENA/SSA- Middle East, North Africa and Sub-Saharan African Countries
US-area: North, Central and South America

Table SV.3, Table SV.4 and Table SV.5 provide interval exposure by age, gender and pathogen, respectively.

The worldwide exposure estimate for gender and age categories is based on the International Medical Statistics (IMS) Medical Database. The IMS Medical database contains patient, diagnosis, and treatment information captured at the time of the patient visit with the physician. This information is provided by the physician and reflects only a sample of total patients. Therefore, the IMS data for age and gender were calculated in percentages and these percentages were applied to the total patient exposure volume based on sales data.

Table SV.3: Estimate of Post-marketing Exposure broken down by Age Group† during reporting period of PSUR #21

			No. of Patients		
Age Group	**JP Area**	**US Area**	**EEA**	**Russia & MENA/SSA**	**Total**
Neonates	468	0	875	-	1,343
Infants	754	0	692	-	1,446
Child	2,677	354	1,445	-	4,476
Adolescent	1,300	446	346	-	2,092
Pediatric Total	5,198	801	3,358	-	9,356
Adults	31,188	50,788	10,520	-	92,497
Elderly	67,575	46,971	6,471	-	121,017
Not Available	-	-	-	3,735	3,735
Total	**103,962**	**98,559**	**20,349**	**3,735**	**226,605**

JP: Japan; US: United States; EEA: European Economic Area; MENA/SSA- Middle East, North Africa and Sub-Saharan African Countries

JP area: Asia and Oceania; US area: North, Central and South America

Neonates (< 1 month), Infants (1 month to < 2 years), Child (2 years to < 12 years), Adolescent (12 years to < 16 years) Pediatric (< 16 years), Adults (16 years to < 65 years), Elderly (> 65 years)

The discrepancy between the total reported and the actual total of the breakdown is due to rounding.

†These numbers are calculated (extrapolated), based on the data described below and the sales figures.

1) JP area: Asia and Oceania. The population figures are based on data from IMS Japan and from Japanese post marketing surveillance (e.g., Use results Surveillance) in Japan. Approximately 65% of patients are classified as elderly and 5% of patients are classified as pediatric patients. The pediatric population figures are based on Japanese post marketing surveillance FUNS01, in which the study age distribution was: neonate 9%, infant 14.5%, child 51.5%, adolescent 25%.

2) US area: North, Central, and South America. The age allocation figures are based on information from Arlington Medical Resources, Inc. The age distribution was: neonate 0.0%, infant 0.0%, child 0.4%, adolescent 0.5% (pediatric total 0.9%), adults 51.5%, elderly 47.6%.

3) For EEA, the population figures are based on cumulative data (n= 667) from the MYRIADE study (a French national observational prospective study on the use of micafungin as prophylactic or curative treatment for invasive fungal infections) and MIAMI study (a German multicenter, prospective non-interventional study for the treatment of IC, EC or prophylaxis of candida infections). The age distribution was: neonate 4.3 %, infant 3.4 %, child 7.1 %, adolescent 1.7 %, adults 51.7 %, elderly 31.8 %.

Based on the above table, the highest exposure per age group globally was in the elderly population followed by the adult and pediatric populations. In the pediatric population, the highest exposure was in children of 2 to <12 years.

In the US and EEA, the data source Antifungal Market Guide* provides the portion of patients by gender. Table SV.4 below represents cumulative exposure data from 2011 to 2013.

*_Antifungal Market Guide. A syndicated clinical audit of hospital systemic antifungal drug usage covering acute care hospitals in the US, Italy, Germany, France, United Kingdom and Spain. The information in the audit is_

Table SV.4: Estimate of Post-marketing Exposure broken down by Gender from 2011 to 2013

Gender	US	EU5†
Female	49%	30%
Male	51%	70%

US: United States; EU5: Italy, Germany, France, United Kingdom and Spain

† In the PSUR 19 (09 Oct 2014 - 08 Oct 2015) it was presented that the gender proportion in the EEA was 34% female and 66% male based on the data of Antifungal Market Guide from 2011 to 2013. However, the actual period of the data source used for the PSUR 19 was from 2010 to 2012.

Table SV.5: Estimated Patient Allocation by pathogen (confirmed only)

Pathogen**	US Allocation	EU5 Allocation
Aspergillus	4.4%	0.4%
Candida (Torulopsis) glabrata	20.5%	44.2%
Candida albicans	58.4%	28.6%
Candida krusei	2.2%	7.8%
Candida lusitaniae	1.1%	2.8%
Candida parapsilosis	4.8%	8.2%
Candida tropicalis	7.6%	7.3%
Cryptococcus neoformans	0.2%	0.0%
Histoplasma capsulatum/duboisii	0.4%	0.1%
Sporothrix schenckii	0.0%	0.5%

US: United States; EU5: Italy, Germany, France, United Kingdom and Spain

**Includes Confirmed Pathogen utilization only

The cumulative exposure broken down by age is shown in Table SV.6. To calculate the cumulative market exposure by age group, the same age factors applied to the interval period were applied to the cumulative data. This is due to the limited availability of historical patient demographic data.

abstracted directly from hospital source documents from a panel of demographically representative acute care hospitals of all sizes, including transplant centers. Users of this audit have the capability to monitor inpatient shares, costs, and the clinical use of systemic antifungal agents. For every therapeutic drug course there is a link between drugs, diagnosis and suspected or confirmed fungal pathogen. The US audit is published twice a year in Mar and Sep and the European data is published once each year in Apr.

Table SV.6: Estimate of Cumulative Post-marketing Exposure broken down by Age Group†

Cumulative – until PSUR 21					
Age group	**JP Area**	**US Area**	**EEA**	**Russia & MENA/SSA**	**Total**
Neonates	5,567	0	4,397	-	9,964
Infants	8,970	0	3,476	-	12,446
Child	31,858	3,196	7,260	-	42,314
Adolescent	15,465	4,023	1,738	-	21,226
Pediatric Total	61,861	7,219	16,871	-	85,950
Adults	371,165	457,855	52,862	-	881,882
Elderly	804,192	423,443	32,515	-	1,260,150
Not Available	-	-	-	11,063	11,063
Total	**1,237,218**	**888,517**	**102,247**	**11,063**	**2,239,045**

JP: Japan; US: United States; EEA: European Economic Area; MENA/SSA: Middle East, North Africa and Sub-Saharan African Countries; PSUR: periodic safety update report

JP area: Asia and Oceania; US area: North, Central and South America; EEA: European Economic Area

Neonates (< 1 month), Infants (1 month to < 2 years), Child (2 years to < 12 years), Adolescent (12 years to < 16 years) Pediatric (< 16 years), Adults (16 years to < 65 years), Elderly (> 65 years)

The discrepancy between the total reported and the actual total of the breakdown is due to rounding.

†These numbers are calculated (extrapolated), based on the data described below and the sales figures.

1) JP area: Asia and Oceania: The population figures are based on data from IMS Japan and from Japanese post marketing surveillance (e.g., Use results Surveillance) in Japan. Approximately 65% of patients are classified as elderly and 5% of patients are classified as pediatric patients. The pediatric population figures are based on Japanese post marketing surveillance FUNS01, in which the study age distribution was: neonate 9%, infant 14.5%, child 51.5%, adolescent 25%.

2) US area: North, Central, and South America. The age allocation figures are based on information from Arlington Medical Resources, Inc. The age distribution was: neonate 0.0%, infant 0.0%, child 0.4%, adolescent 0.5% (pediatric total 0.9%), adults 51.5%, elderly 47.6%.

3) For EEA, the population figures are based on cumulative data (n= 667) from the MYRIADE study (a French national observational prospective study on the use of micafungin as prophylactic or curative treatment for invasive fungal infections) and MIAMI study (a German multicenter, prospective non-interventional study for the treatment of IC, EC or prophylaxis of candida infections). The age distribution was: neonate 4.3 %, infant 3.4 %, child 7.1 %, adolescent 1.7 %, adults 51.7 %, elderly 31.8 %.

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

Astellas 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, Astellas 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.

Module SVII. Identified and potential risks

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

Section SVII.1 is not applicable, as this RMP is not an initial RMP submission.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not Applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not Applicable

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

Considering the guidance provided in Good Pharmacovigilance Practices (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 (IV 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: 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 (area under the plasma concentration-time curve [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 risks, 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)

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 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 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 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 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 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 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 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

DIC: disseminated intravascular coagulation.

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

Table 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)

DIC: disseminated intravascular coagulation.

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

Table 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

DIC: disseminated intravascular coagulation.

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

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

	Number of Subjects (Incidence [%] within age group)		
	< 16 yrs-old	**16-64yrs-old**	**≥ 65 yrs-old**
Category	**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]. 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

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 (MEC50/90, ≤0.008/0.015 µg/mL) and other echinocandins at ≤0.06 µg/mL. These isolates displayed WT minimum effective concentration (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 μg/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

Not applicable

Module SVIII. Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hemolytic AEs including disseminated intravascular coagulation
Important potential risks	• Development of resistant strains
Missing information	• None

AEs: adverse events

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

Table 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 DIC

DIC: disseminated intravascular coagulation; Adverse event follow-up questionnaires are provided in [Annex 4]

Table Part III.2: Other forms of routine pharmacovigilance activities

Activity	Objective(s)/Description	Milestone(s)
None	NA	NA

III.2 Additional pharmacovigilance activities

Table Part III.3: 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 located in Europe, North America, and other regions).
Milestones	Each PSUR in line with applicable regulatory requirements

MIC: minimum inhibitory concentration; PSUR: periodic safety update report

III.3 Summary table of additional pharmacovigilance activities

Table Part III.4: 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.

NA: not applicable.

PART IV. PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorization				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V. RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Hemolytic AEs including DIC	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 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.
Development of resistant strains	Routine risk communication: • SmPC Section 5.1

AE: adverse event; DIC: Disseminated intravascular coagulation; PL: package leaflet; SmPC: summary of product characteristics

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.2.1 Removal of additional risk minimization activities

Table Part V.2: Removal of additional risk minimization activities

Activity	Safety concern(s) addressed	Rationale for the removal of additional risk minimization activity
Nurse Administration and Monitoring Guide	• Hemolytic AEs • Allergic-Like/Possible Histamine-Mediated AEs • Hepatic AEs • Renal AEs • Relevance in humans of the development of liver tumors in rats	The administration guide has been retired since it was designed as the interventional tool that was targeted towards nurses. Nurses are the main contributors to minimize the risk of allergic-like AEs in the health care delivery system of Mycamine. The effectiveness checks have shown that allergic-like reactions are a well-known risk by HCPs. Allergic-like/possible histamine-mediated AEs are no longer a safety concern in the RMP (See Section SVII.2).
Updated Prescriber's Checklist	• Hemolytic AEs including DIC • Hepatic AEs • Renal AEs • Relevance in humans of the development of liver tumors in rats	Prescriber's Checklist has been retired: • The current effectiveness study (9463-PV-0002) results indicated a higher knowledge level of the hepatic precautions (potential risk of liver tumor and restricted indications) for use of Mycamine by the HCPs compared to the previous effectiveness studies conducted in 2013 and 2017, while the percentage of the HCPs aware of the Prescriber's Checklist has been decreasing. • The top three sources of information used by HCPs to learn about the appropriate indication, precautions for use and potential risks for Mycamine in the more aligned countries were the summary of product characteristics (92.6%), Prescriber's Checklist (44.4%), and professional society or congress (34.6%), whereas the top three sources for HCPs practicing in the less aligned country was the summary of product characteristics (91.3%), the EMA website (47.8%), and clinical practice guidelines (39.1% vs. 7.4% for more aligned countries). These results suggest that the Prescriber's Checklist is unlikely to play a significant role in influencing HCP behavior. Hepatic AEs, Renal AEs and Relevance in humans of the development of liver tumors in rats are no longer a safety concern in the RMP (See Section SVII.2).

AEs: adverse events; DIC: disseminated intravascular coagulation; EMA: European medicines agency; HCPs: healthcare professionals; RMP: risk management plan; SmPC: summary of product characteristics

V.3 Summary of Risk Minimization Measures

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hemolytic AEs including DIC	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific standardized follow-up questionnaires Additional pharmacovigilance activities: • None
Development of resistant strains	Routine risk minimization measures: • SmPC Section 5.1 Additional risk minimization measures: • None	Additional pharmacovigilance activities: • International antifungal surveillance study

AEs: adverse events; DIC: disseminated intravascular coagulation; PL: package leaflet; SmPC: summary of product characteristics

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 in adults, adolescents ≥ 16 years of age and elderly for treatment of invasive candidiasis and for oesophageal candidiasis in patients for whom intravenous therapy is appropriate. In children (including neonates) and adolescents < 16 years of age, Mycamine is indicated for invasive candidiasis only. Mycamine is being used for prophylaxis of *Candida* infection in patients (adults, elderly, adolescents and children) undergoing

allogeneic hematopoietic 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). Mycamine 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:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000734/human_med_000911.jsp

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 analyzed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Mycamine is not yet available, it is listed under 'missing information' below.

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 AEs including DIC
Important potential risks	• Development of resistant strains
Missing information	• None

AEs: adverse events; DIC: disseminated intravascular coagulation

II.B Summary of important risks

Important identified risk: Hemolytic AEs including DIC	
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; 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. Additional risk minimization measures: • None

Important identified risk: Hemolytic AEs including DIC	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

AEs: adverse events; PL: package leaflet; SmPC: summary of product characteristics; DIC: disseminated intravascular coagulation

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 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.

SmPC: summary of product characteristics

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.

PART VII. ANNEXES

Table of Contents

Annex 4 Specific adverse event 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 <Astellas product>. 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.