RISK MANAGEMENT PLAN:

EU QPPV AND CONTACT PERSON FOR THIS RMP

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

EU Qualified Person for Pharmacovigilance (QPPV) name:	Guy Demol
EU QPPV signature:	PPD
Date of signature:	8 MAY 2018

Contact person for this RMP:	PPD
Contact person e-mail address:	
Contact person telephone number:	

RISK MANAGEMENT PLAN (RMP)

Caspofungin Acetate

Powder for concentrate for solution for infusion

Version: 3.2

DATE OF THIS RMP: 08-MAY-2018

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LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CT	Computed Tomography
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study
PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term

QD	Once Daily
QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TIW	Three Times Per Week
WBC	White Blood Cell Count

PART I PRODUCT(S) OVERVIEW

Table 1 Active Substance Information

Active substance(s):	Caspofungin acetate (hereafter referred to as "[CANCIDAS]")
Pharmacotherapeutic group(s) (ATC code(s)):	JO2AX04
Name of Marketing Authorization Holder or Applicant:	Merck Sharp & Dohme Ltd.
Number of medicinal products to which this RMP refers:	1
Product(s) concerned:	CANCIDAS®

Data lock point for this RMP: 01-JUN-2017 Version number: **3.2**

Date of final sign-off: **08-MAY-2018**

Administrative information on the RMP

Table 2 List Of All Parts And Modules Of The RMP With Date And Version of the RMP when the Part / Module was Last (Updated and) Submitted

RMP PART / MODULE		Date last updated for submission (sign off date)	Version number of RMP when last updated
PART II	SAFETY SPECIFICATION		
Module SI	Epidemiology of the indication(s) and target population(s)	23-Feb-2018	3.0
Module SII	Non-clinical part of the safety specification	08-MAY-2018	3.2
Module SIII	Clinical trial exposure	23-Feb-2018	3.0
Module SIV	Populations not studied in clinical trials	08-MAY-2018	3.2
Module SV	Post-authorization experience	23-Feb-2018	3.0
Module SVI	Additional EU requirements for the safety specification	26-Mar-2018	3.1
Module SVII	Identified and potential risks	08-MAY-2018	3.2
Module SVIII	Summary of the safety concerns	08-MAY-2018	3.2
PART III	PHARMACOVIGILANCE PLAN	08-MAY-2018	3.2
PART IV	PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES	23-Feb-2018	3.0
PART V	RISK MINIMIZATION MEASURES	08-MAY-2018	3.2
PART VI	SUMMARY OF THE RISK MANAGEMENT PLAN	08-MAY-2018	3.2
PART VII	ANNEXES		
ANNEX 2	Current or proposed SmPC / PIL	23-Feb-2018	3.0
ANNEX 3	Worldwide marketing authorization status by country	23-Feb-2018	3.0
ANNEX 4	Synopsis of clinical trial programme	23-Feb-2018	3.0
ANNEX 5	Synopsis of pharmacoepidemiological study programme	23-Feb-2018	3.0
ANNEX 6	Protocols for proposed and on-going studies in in RMP part III	23-Feb-2018	3.0
ANNEX 7	Specific adverse event follow-up forms	23-Feb-2018	3.0
ANNEX 8	Protocols for proposed and on-going studies in RMP part IV	23-Feb-2018	3.0
ANNEX 9	Synopsis of newly available study reports for RMP parts III-IV	23-Feb-2018	3.0
ANNEX 10	Details of proposed additional risk minimization activities	23-Feb-2018	3.0
ANNEX 11	Mock up examples	23-Feb-2018	3.0
ANNEX 12	Other supporting data	23-Feb-2018	3.0

Changes from previous RMP version

The previous RMP version (Cancidas RMP version 2.0) was approved in 2008. Merck Sharp & Dohme (MSD) is updating the RMP to version 3.2 due to the addition of a new safety concern of Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN). The previously identified important risk of histamine-mediated allergic reaction has been broadened to 'hypersensitivity reactions' and now includes both histamine-mediated allergic reaction and SJS/TEN. Additional changes concern the update of the template (Rev. SVI.2).

Name of EU QPPV and Contact person for this RMP:

The name and signature of the EU QPPV and the name and contact information of the Contact person for this RMP are provided as a separate component.

Overview of EU-RMP versions:

Version number of last agreed RMP:

Version number	2.0
Agreed within	EMEA/H/C/0379/II/35 New data on the pharmacokinetics, safety and efficacy of caspofungin at three times the licensed daily maintenance dose (i.e., 150 mg daily) in adult patients was included in sections 4.2, 4.8 and 5.1 of the SmPC and section 4 of the PIL, to appropriately reflect the experience of caspofungin at this higher dose.
Version number	1.0
Agreed within	EMEA/H/C/0379/II/33 Submission of new paediatric data on the pharmacokinetics, safety and efficacy of Caspofungin, to support the use of Cancidas in children and creation of RMP.

Current RMP version(s) under evaluation:

EU RMP version 2.1 is still under evaluation by the Agency. EU RMP version 3.2 has been created to address agency comments from version 3.1.

Table 3 Product Description

Invented name(s) in the European Economic Area (EEA):	CANCIDAS®
Authorization procedure:	Centralised
Brief description of product:	
Chemical class:	Caspofungin acetate (MK-0991, CANCIDAS®), a member of class of antifungal agents known as the echinocandins, is an active, semisynthetic inhibitor of β-1,3-D-glucan, an important component of the fungal cell wall.
Summary of mode of action:	By targeting the fungal cell wall (as opposed to the fungal cell membrane), the echinocandins exhibit a unique mechanism of action relative to the other currently approved antifungal agents.
Important information about its composition:	Caspofungin for Injection: 50 or 70 mg lyophilized powder (plus allowance for overfill) is a single-dose vial for reconstitution. Caspofungin is a macrocyclic lipopeptide that is provided as a diacetate salt. The current pH 6, lyophilized formulation of caspofungin is supplied in a 10-mL vial. It must be reconstituted before use.
Indication(s) in the EEA:	
Current:	Currently, CANCIDAS® is approved for use in patients for the following indications in EEA • Treatment of invasive candidiasis in adult or paediatric patients; • Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy; • Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult or paediatric patients.
Proposed:	Not applicable
Posology and route of administration in the EEA:	
Current:	Adult patients A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, caspofungin 70 mg daily is recommended. No dosage adjustment is necessary based on gender or race. Paediatric patients (12 months to 17 years) In paediatric patients (12 months to 17 years of age), dosing should be based on the patient's body surface area. For all indications, a single 70-mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). If the 50-mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg).

Table 3 Product Description

	The safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age. Caution is advised when treating this age group. Limited data suggest that caspofungin at 25 mg/m^2 daily in neonates and infants (less than 3 months of age) and 50 mg/m^2 daily in young children (3 to 11 months of age) can be considered. Duration of treatment Duration of empirical therapy should be based on the patient's clinical response. Therapy should be continued until up to 72 hours after resolution of neutropaenia (ANC≥500). Patients found to have a fungal infection should be treated for a minimum of 14 days and treatment should continue for at least 7 days after both neutropaenia and clinical symptoms are resolved. Duration of treatment of invasive candidiasis should be based upon the patient's clinical and microbiological response. After signs and symptoms of invasive candidiasis have improved and cultures have become negative, a switch to oral antifungal therapy may be considered. In general, antifungal therapy should continue for at least 14 days after the last positive culture. Duration of treatment of invasive aspergillosis is determined on a case by case basis and should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. In general, treatment should continue for at least 7 days after resolution of symptoms. The safety information on treatment durations longer than 4 weeks is limited. However, available data suggest that caspofungin continues to be well tolerated with longer courses of therapy (up to 162 days in adult patients and up to 87 days in paediatric patients).
Proposed:	Not applicable
Pharmaceutical form(s) and strength(s):	
Current:	Powder for concentrate for solution for infusion, 50 mg/vial Powder for concentrate for solution for infusion, 70 mg/vial
Proposed:	Not applicable
Country and date of first authorization worldwide:	14 December 2000, Mexico
Country and date of first launch worldwide:	February 2001, United States
Country and date of first authorization in the EEA:	24 October 2001 (centralized procedure)
Is the product subject to additional monitoring in the EU, as per Regulation (EC) 726/2004, Article 23?	**No**

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND THE TARGET POPULATIONS

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 2.0

Indication: Currently, CANCIDAS® is approved for use in patients for the following indications (dependent on current local approval status of each indication):

- Treatment of invasive candidiasis in adult or paediatric patients;
- Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy;
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult or paediatric patients.

SI.1 Epidemiology of the Disease

The epidemiology of the various indications for which caspofungin acetate is currently approved are outlined below.

Indication: Invasive Aspergillosis

Aspergillus species are the most commonly isolated invasive molds. Invasive aspergillosis is a rapidly progressive, often fatal pulmonary infection that may disseminate to the brain, skin, and bone. This infection occurs almost exclusively in patients who are severely immunosuppressed such as people who have had an organ or a stem cell transplant [Ref. 5.4: 04SXF4].

Incidence and prevalence:

The incidence of invasive aspergillosis reflects disease states and treatments that result in prolonged neutropenia and immunosuppression. Evidence suggests a bimodal time distribution of invasive aspergillosis occurrence following stem cell transplant which reflects different risk factors. Early invasive aspergillosis has been linked to neutropenia, and late invasive aspergillosis occurs in patients with high-dose immunosuppressive therapy for

GVHD. *Aspergillus* infections have been reported in 2 to 26% of HSCT recipients and in 1 to 15% of organ transplant recipients [Ref. 5.4: 00W8W0].

Demographics of the target population:

The demographics of individuals with aspergillosis infection are consistent with the demographics of individuals with immunocompromised conditions with which this infection is associated.

Risk factors for the disease:

Well-established risk factors for invasive aspergillosis include underlying lung disease, prolonged neutropenia, immunosuppressive therapy, corticosteroid therapy, allogenic hematopoietic stem cell transplantation (HSCT), and graft versus-host disease (GVHD) and its treatment, solid organ transplant, haematologic malignancy, cytotoxic drugs and AIDS. [Ref. 5.4: 00W895, 04SXF4] HSCT recipients more frequently develop disseminated disease, while persons with hematologic malignancies more commonly develop diffuse invasive pulmonary disease, as do persons with AIDS [Ref. 5.4: 00W895].

Main treatment options:

Voriconazole is the first-line treatment for invasive aspergillosis. In individuals who cannot tolerate or respond to voriconazole, other treatment options include the following: itraconazole, lipid amphotericin B formulations, caspofungin, micafungin and posaconazole.

Mortality and morbidity (natural history):

Invasive aspergillosis is a rapidly progressive, often fatal pulmonary infection that may disseminate to the brain, skin, and bone. The outcome of invasive aspergillosis remains poor and is associated with significant mortality. In a large, systematic literature review of 1,941 cases, the overall case fatality rate was 58% and the case fatality rate was highest in bone marrow transplant recipients (86.7%) and for patients with central nervous system or disseminated aspergillosis (88.1%). Case fatality was generally consistent across age groups though tended to be higher in the youngest age group of patients 20 years old or younger [Ref. 5.4: 03R2S0]. At the time of this report, newer treatments, such as azoles, were not available or the availability was limited [Ref. 5.4: 03R2S0].

Indication: Invasive Candidiasis

Invasive candidiasis occurs when *Candida* enters the bloodstream by direct penetration from epithelial tissues causing bacteremia and then spreads throughout the body. There are two forms of invasive candidiasis, candidemia and disseminated candidiasis. Candidemia is the isolation of *Candida* species in a blood culture [Ref. 5.4: 04S9XW]. Disseminated candidiasis is associated with multiple deep organ infections and can be difficult to diagnose. [Ref. 5.4: 04S9XW]

Incidence and prevalence:

The incidence of IFI, most often caused by *Candida* and *Aspergillus* species, has increased in North America and Europe over the past decades. *Candida* blood infections have steadily increased since the 1980s and account for 8-15% of all blood infections [Ref. 5.4: 00W8J9]. The incidence of candidemia has been increasing or stable in most regions, although there have been reports of declining or stable incidence rates in high incidence areas as a result of the introduction of improvements in disease management and hygiene [Ref. 5.4: 04T70M, 044763, 04T5S3].

Globally, there are more than 250,000 cases of invasive candidiasis each year. The incidence of candidemia ranges between 2 and 14 per 100,000 in population-based studies [Ref. 5.4: 04T70M, 00W895]. *Candida* species are the most common cause of IFIs in hospitalized patients and the fourth most common cause of nosocomial bloodstream infection (BSI) in the US. Rates have been higher in infants (75 per 100,000) and the elderly (45 per 100,000) [Ref. 5.4: 00W8H5].

Candidemia is the fourth most common catheter-related BSI in Europe. The incidence of candidemia in Europe, based upon a few small studies, ranges from 1.4 cases per 100,000 population between to 4.9 cases per 100,000 population [Ref. 5.4: 00W890, 00W8J8, 00W88Z].

Previously, *C. albicans* was the most common pathogen [Ref. 5.4: 00W8J9]. In more recent studies, *C. albicans* accounts for only half of the isolates. In northern Europe, the US and Canada, *C. glabrata* has become a leading pathogen and in Southern Europe, Asia and South America, *C. parapsilosis* has become the more prominent pathogen [Ref. 5.4: 04T70M, 00W8W3, 00W892]. The shift in pathogenic *Candida* species may be due to the increased use of azole prophylaxis, although this remains unclear.

Demographics of the target population:

The highest rates in the population under surveillance occurred in infants (75 per 100,000) and the elderly (45 per 100,000).

Risk Factors:

Risk factors for invasive candidiasis include: critical illness with particular risk among patients with long-term ICU stay, abdominal surgery, with particular risk among patients who have anastomotic leakage or have had repeat laparotomies, acute necrotizing pancreatitis, hematologic malignant disease, solid-organ transplantation, solid-organ tumors, neonates, particularly those with low birth weight and preterm infants, use of broad spectrum antibiotics, presence of central vascular catheter, total parenteral nutrition, hemodialysis, glucocorticoid use or chemotherapy for cancer, Candida colonization, particularly if multifocal [Ref. 5.4: 04T70M, 00W895].

Main treatment options:

Per recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, echinocandins (caspofungin, anidulafungin, micafungin) are the first-line treatment for candidiasis. Additionally, Infectious Diseases Society of America (IDSA) guidelines note that echinocandins are the preferred treatment for unstable patients, patients receiving prior azole prophylaxis, and patients with documented *C. glabrata* or *C. krusei* infections. Azoles (fluconazole, voriconazole and posaconazole) are also used to treat candidiasis infection. Finally, Amphotericin B is another treatment option, and has been used for decades to treat candidiasis infection, but is associated with significant nephrotoxicity. At this time, antifungal prophylaxis should be limited to patients with gastrointestinal anastomotic leakage, patients undergoing transplantation of the pancreas or the small bowel, selected patients undergoing liver transplantation at high risk for candidiasis and extremely low-birthweight neonates in settings with high incidence of neonatal candidiasis [Ref. 5.4: 04T70M].

Mortality and morbidity (natural history):

Candida infections have been associated with significant mortality, especially among critically ill patients. Worldwide, invasive candidiasis is the cause of more than 50,000 deaths each year *[Ref. 5.4: 04T70M]*. The crude mortality rate of these infections is high (40-75%), and the attributable mortality of candidemia has been estimated at 25%-38% [Ref. 5.4: 00W9WX]. Indication: Empirical treatment of presumed fungal infections (such as Candida and Aspergillus spp.) in febrile, neutropenic adult patients.

As diagnostic tests for confirming type of fungal infection have imperfect precision and can take time, patients must often be treated based upon presumed fungal infection.

Indication: Oropharyngeal Candidiasis

Oropharyngeal candidiasis (OPC) is an opportunistic fungal infection that affects the oral cavity, almost always caused by *Candida albicans*. There are four types of OPC: 1) pseudomembranous (thrush), erythematous, 3) hyperplastic and 4) denture-induced stomatitis [Ref. 5.4: 043375]. Although OPC is defined as superficial candidiasis with shallow levels of tissue invasion, the infection can progress to systemic candidiasis in immunocompromised patients.

Incidence and prevalence:

Candida species are common and often do not affect people. Oropharyngeal candidiasis affects 15%-60% of people with hematological or oncological malignancies during periods of immunosuppression. Oropharyngeal candidiasis occurs in 7%-48% of people with human immunodeficiency virus (HIV) infection and in over 90% of those with advanced disease [Ref. 5.4: 00W8J6]. Oropharyngeal candidiasis is among the most common opportunistic infections in HIV-infected patients, and increases in frequency and intensity as the patient's CD4 cell count decreases. Oropharyngeal candidiasis is often one of the first clinical signs of underlying HIV infection and will occur in 50% to 95% of all HIV-infected persons at some

point during their progression to acquired immunodeficiency syndrome (AIDS) [Ref. 5.4: 00W898]. Oropharyngeal candidiasis is also a common manifestation of chronic mucocutaneous candidiasis, and also occurs in patients with lymphoma, those undergoing steroid therapy, and in transplant recipients.

Demographics of the target population:

OPC can occur in normal newborns. However, OPC occurs more frequently and with greater severity in individuals with a compromised immune system, especially, in individuals with HIV infection/AIDS. In patients with HIV/AIDS, most cases of OPC occur in males ages 15-44 years.

Risk factors for the disease:

OPC is an opportunistic infection with risk factors including conditions associated with a weakened or compromised immune system such as solid organ or stem cell transplants and HIV-infection/AIDS. Other risk factors include hematologic disorders, broad-spectrum antibiotic use, inhaled or systemic corticosteroids, xerostomia, diabetes, wearing dentures, obturators or other orthodontic appliances and smoking [Ref. 5.4: 043375].

Main treatment options:

Clotrimazole troches and nystatin suspension usually provide effective treatment. If infections do not respond to these treatments, systemic antifungals may be necessary. The options for systemic antifungals include: fluconazole, miconazole itraconazole, and posaconazole. In infants and children, nystatin is less effective than the azoles [Ref. 5.4: 043375].

Mortality and morbidity (natural history):

Individuals with OPC infection usually have painless, white patches in the mouth. OPC infections spreading to the esophagus (referred to as esophageal candidiasis) may be associated with pain and difficulty swallowing. OPC has a low attributable mortality. However, OPC infection can, but rarely, progress to invasive candidiasis.

SI.2 Concomitant Medication(s) in the Target Population

For these indications, concomitant medications include those treatments commonly used for solid organ transplant, stem cell transplant and HIV.

SI.3 Important Co-morbidities Found in the Target Population

Indication: Invasive Aspergillosis

This infection occurs almost exclusively in patients who are severely immunosuppressed such as people who have had an organ or a stem cell transplant.

In a six-year multi-center study in France, the incidence of invasive aspergillosis was 8% (95% confidence interval [CI]: 6.5-9.5) in acute myeloblastic leukemia and 6.3% (95% CI: 4.3-8.3) in acute lymphocytic leukemia. Incidence was 12.8% (95% CI: 10.8-14.8) following allogenic stem cell transplantation and 1.1% (95% CI: 0.7-1.5) following autologous stem cell transplantation [Ref. 5.4: 00W896].

Incidence of invasive aspergillosis varies according to type of organ transplant. Between 3.3 and 16% of lung transplant recipients develop this disease [Ref. 5.4: 00W8H4]. In a prospective cohort study, the incidence of invasive aspergillosis was 11% following heart-lung transplant [Ref. 5.4: 00W896]. In liver transplant patients, 1.6 to 7.6% of patients developed invasive aspergillosis [Ref. 5.4: 00W8W0]. Liver transplant recipients are also uniquely predisposed to dissemination of infection beyond the lungs, which occurs in ~50-60% of cases. In certain low-risk groups such as renal transplant recipients, invasive aspergillosis has been reported in ~0.4% and in up to 4% of patients [Ref. 5.4: 00W896, 00W8W0].

Indication: Invasive Candidiasis

Invasive candidiasis infection occurs in patients with critical illness with particular risk among patients with long-term ICU stay, abdominal surgery, patients who have anastomotic leakage or have had repeat laparotomies, acute necrotizing pancreatitis, hematologic malignant disease, solid-organ transplantation, solid-organ tumors, neonates with low birth weight and preterm infants, patients with use of broad spectrum antibiotics, patients with presence of central vascular catheter, total parenteral nutrition, hemodialysis, or glucocorticoid use or chemotherapy for cancer [Ref. 5.4: 04T70M, 00W895].

Indication: Oropharyngeal Candidiasis

OPC occurs more frequently and with greater severity in individuals with a compromised immune system, especially, in individuals with HIV infection/AIDS, patients being treated for malignancies.

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 3.2

Table 4 Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Administration of caspofungin in monkeys resulted in very slight (approximately 2-3-fold) increases in transaminase values (alanine aminotransferase [ALT], and/or aspartate aminotransferase [AST]). These effects on transaminase values did not increase despite continued treatment of up to 27 weeks duration. There were no consistent histopathologic changes that correlated with these increases in transaminase values (scattered foci of subcapsular necrosis occurred in some animals in a 5-week study; however, no histopathologic changes occurred in a 27-week study at similar doses). There were no effects on transaminase values in rats administered caspofungin for up to 27 weeks.	Elevations in serum ALT or AST have occasionally been seen in healthy volunteers and patients administered caspofungin (see Section 1.5.2) in clinical trials and postmarketing use. Notably, concomitant use of caspofungin with cyclosporine has been identified as a unique risk factor in patients and healthy volunteers.
Caspofungin is a lipopeptide that fits into the category of basic polypeptides that are often effective histamine releasers. In non-clinical safety assessment studies in rats and monkeys, rapid intravenous infusion of caspofungin was shown to cause physical signs related to histamine release. Pretreatment with antihistaminic agents significantly diminished these effects and prevented a lethal response. Infusion of an analogue of caspofungin to monkeys also caused these signs; however, the signs were reversed upon injection of the antihistamine, cyproheptadine with a 70-mg dose.	Signs of histamine release have occasionally been seen in healthy volunteers and patients administered caspofungin (see Section 1.5.2) in clinical trials and postmarketing use. In an effort to avoid these events, it is mandated that caspofungin never be administered by bolus infusion. Caspofungin should only be administered by a slow infusion over an approximately 1-hour time frame.

Table 4 Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Irritation at the site of intravenous injection occurred in monkeys and rats administered repeated daily doses of caspofungin. The irritation consisted of inflammatory changes of the vessel wall and subcutaneous tissues that were sometimes severe, and in some cases thrombosis in the vascular lumen. It was evident that the phenomenon was related to extravasation of the dosing solution, since refinement of the intravenous injection technique and pre- and post-dose flushing of the catheter and/or needle decreased the incidence and severity of the change. Subcutaneous administration of the dosing solution in rabbits caused varying degrees of inflammatory change in the subcutis and skin, with transmural necrosis of the skin in some cases.	Signs of local irritation at the site of caspofungin infusion have occasionally been seen in healthy volunteers and patients administered caspofungin in clinical trials and postmarketing use. In most patients, the event has been reported as a mild, transient event.
Caspofungin was shown to be potentially embryotoxic in rats and rabbits. Findings included incomplete ossification of the skull and torso and an increased incidence of cervical rib in rats. An increased incidence of incomplete ossification of the talus/calcaneus was seen in rabbits. Caspofungin also produced increases in resorption in rats and rabbits and peri-implantation losses in rats. These findings were observed at doses that produced exposures similar to those seen in patients treated with a 70-mg dose. Caspofungin crossed the placental barrier in rats and rabbits and was detected in the plasma of fetuses of pregnant animals dosed with caspofungin. Caspofungin is also excreted in the milk of lactating animals.	There are no adequate and well-controlled studies of caspofungin in pregnant or breast-feeding women. Patients who were pregnant or breast-feeding were excluded from clinical trials. Caspofungin should not be used in pregnancy unless clearly necessary, as the potential risk to the human fetus is unknown. Women receiving caspofungin should also not breast-feed.
Mutants of Candida with reduced susceptibility to caspofungin have been generated in the laboratory. Similar observations were made in a study in mice infected with C. albicans and treated with orally administered doses of caspofungin. Specifically, it has been determined that mutations in the Candida FKS1 gene confer reduced susceptibility to caspofungin	Mutants of Candida with reduced susceptibility to caspofungin have been identified in some patients during treatment. The incidence of drug resistance by various clinical isolates of Candida and Aspergillus species is currently low, and a correlation between MIC values for caspofungin and clinical outcome has not been established. The emergence of caspofungin-resistant Candida or Aspergillus isolates could potentially result in clinical failure in the patient and cross-resistance to other echinocandin antifungal drugs.

As it pertains to the pediatric population, a 5-week intravenous toxicity study was conducted in infant rhesus monkeys at caspofungin doses used in repeat-dose studies in adult monkeys, and there were no treatment-related findings as a result of treatment with caspofungin. At this point, the MAH does not believe there is a need for additional non-clinical data with caspofungin.

Conclusions on Non-clinical Data

Table 5 Summary of Important Safety Concerns from Non-clinical Data

Important identified risks (confirmed by clinical/postmarketing data)	▪ Increase in liver enzymes ▪ Hypersensitivity reactions including histamine-mediated allergic reactions ▪ Drug resistance
Important potential risks	▪ None
Missing information	▪ None

MODULE SIII CLINICAL TRIAL EXPOSURE

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 2.0

SIII.1 Brief Overview of Development

Caspofungin acetate (CANCIDAS®, MK-0991, L-000743872; hereafter referred to as caspofungin) is an antifungal agent from the echinocandin class of compounds. It was initially licensed for human use in December, 2000 and is now registered in over 95 countries worldwide. Caspofungin is indicated for the treatment of adult and pediatric patients for one or more of the following: (1) invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole); (2) esophageal candidiasis; (3) candidemia and other Candida infections, including intra-abdominal abscesses, peritonitis, and pleural space infection; and (4) empirical therapy of suspected invasive fungal infections in febrile, neutropenic patients. In the adult and pediatric populations, the indications may vary by country. In the pediatric population, the age range for indications may also vary by country. The approved dose of caspofungin in adults is 50 mg daily (following a 70-mg loading dose on Day 1 in patients with proven or suspected invasive fungal infections). Pediatric dosing is based on body-surface-area (BSA) dosing. In pediatric patients (12 months to 17 years of age), the approved dose of caspofungin is 50 mg/m^2 daily (following a 70-mg/m^2 loading dose on Day 1). The maximum daily dose in pediatric patients should not exceed 70 mg.

SIII.2 Clinical Trial Exposure

Clinical Trial Exposure by Duration of Exposure

Clinical Trial Exposure

The clinical trial exposure is listed separately based on study phase (Phase I vs. Phase II-III trials). The experience includes data from healthy adult subjects (enrolled in Phase I studies), adult patients (enrolled in Phase II-III trials), and pediatric patients (enrolled in Phase II-III trials). The Phase II-III data in adults are limited to patients receiving caspofungin monotherapy at the minimum of the approved dose (50 mg daily).

Phase I Studies

All Phase I studies that were completed were in healthy adult subjects. No Phase I pediatric studies were conducted.

Table 6 Duration of Caspofungin Treatment by Daily Dose for Phase I Healthy Adult Studies

Treatment Group	Days of Treatment				Total Subject Days on Caspofungin	Range of Treatment Duration on Caspofungin (Days)	Mean Treatment Duration on Caspofungin (Days)	Person-Time (in years)
	1	2 to 7	8 to 14	>15				
Caspofungin Alone								
Total subjects on caspofungin <50 mg (N=48) [*†]	2	14	32	0	492	1 to 14	10.3	1.35
Total subjects on caspofungin 50 mg (N=114) [††]	0	4	105	5	1517	2 to 16	13.3	4.2
Total subjects on caspofungin >50 mg (N=176) [‡*]	123	6	22	25	1110	1 to 21	6.3	3.0
Caspofungin and Other Drugs								
Total subjects on caspofungin <50 mg (N=8)	0	8	0	0	24	3	3.0	0.1
Total subjects on caspofungin 50 mg (N=69) [§ ‡‡]	0	2	55	12	905	2 to 16	13.1	2.5
Total subjects on caspofungin >50 mg (N=41)	3	14	24	0	335	1 to 11	8.2	1.0

† Twelve subjects received a loading dose of 70 mg on Day 1 and then received 40 mg daily of caspofungin for remainder of the treatment period (Study 063).

†† Nineteen subjects received a loading dose of caspofungin 70 mg on Day 1, followed by caspofungin 50 mg daily for remainder of treatment period; 28 subjects received 50 mg daily.

‡ Thirty one subjects received single doses of caspofungin <50 mg in addition to single doses of caspofungin >50 mg.

§ Eight subjects received a loading dose of caspofungin 70 mg on Day 1, followed by caspofungin 50 mg daily for remainder of treatment period; 26 subjects received 50 mg daily without the loading dose.

* In Protocols 001 and 057, subjects were categorized based on the highest dose received.

‡‡ In Protocol 035, subjects who received rifampin alone on Days 1 to 14 were also accounted for in subjects who received rifampin + caspofungin on Days 15 to 28.

Phase II-III Studies

a) Adult Studies: Exposure estimates include all pivotal Phase II/III Protocols in support of the licensed adult indications for caspofungin [Protocols 003, 004, 007, 020, 014, 019, 026, and 801].

Table 7 Clinical Trial Exposure to Caspofungin by Duration of Exposure (TOTALS) - Protocols 003, 004, 007, 020, 014, 019, 026, and 801

Minimum Exposure	Persons	Person-Time (in years)
>0 day	1285	50.72
>1 week	928	45.59
>2 weeks	365	27.90
>3 weeks	173	18.72
>4 weeks (1 month)	92	13.11
>8 weeks (2 months)	27	6.18

Exposure is defined as the summation of any day when any dose of study therapy was taken for the particular groups presented.

Table 8 Clinical Trial Exposure to Caspofungin by Daily Maintenance Dose (TOTALS) - Protocols 003, 004, 007, 020, 014, 019, 026, and 801

Daily Maintenance Dose‡	Persons	Person-Time (in years)
<50 mg	46	1.08
50 mg	1043	36.13
>50 mg to ≤70 mg	189	6.90
>70 mg to ≤100 mg	8	0.59
>100 mg to ≤149 mg	5	0.02
≥150 mg	100	3.88

† Excludes 70 mg loading dose on Day 1, if administered.
‡ Patients receiving different dosing regimens during the treatment course may appear in multiple rows.

Table 9 Clinical Trial Exposure to Caspofungin by Daily Maintenance Dose (TOTALS) - Protocols 003, 004, 007, 020, 014, 019, 026, and 801

Daily Maintenance Dose‡	Persons	Person-Time (in years)
<50 mg	46	1.08
50 mg	1043	36.13
>50 mg to ≤70 mg	189	6.90
>70 mg to ≤100 mg	8	0.59
>100 mg to ≤149 mg	5	0.02
≥150 mg	100	3.88

† Excludes 70 mg loading dose on Day 1, if administered.
‡ Patients receiving different dosing regimens during the treatment course may appear in multiple rows.

Table 10 Clinical Trial Exposure by Age Group and Gender - Protocols 003, 004, 007, 020, 014, 019, 026, and 801

	Person		Person-Time (in years)	
Age Group (years)	Male	Female	Male	Female
<18	5	1	0.29	0.00
18 to 64	649	376	25.85	14.14
≥65	142	112	5.83	4.61

Table 11 Clinical Trial Exposure by Race - Protocols 003, 004, 007, 020, 014, 019, 026, and 801

Race	Persons	Person-Time (in years)
White	896	37.49
Black	83	2.89
Asian	48	2.38
Hispanic	169	5.40
Multiracial	12	0.46
Other	77	2.10

Table 12 Clinical Trial Exposure by Special Populations (Indications) - Protocols 003, 004, 007, 020, 014, 019, 026, and 801*

Population/Indication	Persons	Person-Time (in years)
Invasive Aspergillosis	127	11.04
Esophageal Candidiasis	276	7.99
Invasive Candidiasis	318	11.69
Persistent Fever & Neutropenia (Empirical Therapy)	564	20.00
*Subjects who were Pregnant/ Breastfeeding, or who had hepatic impairment were excluded from clinical development		

b) Pediatric Studies: All completed pediatric protocols for caspofungin are included [Protocols 033, 042, 043, 044, 058].

Table 13 Clinical Trial Exposure by Duration - Protocols 033, 042, 043, 044, and 058

Minimum Exposure	Persons	Person-Time (in years)
>0 day	171	5.68
>1 week	99	4.80
>2 weeks	40	3.13
>3 weeks	20	2.18
>4 weeks (1 month)	13	1.68
>8 weeks (2 months)	4	0.82

Table 14 Clinical Trial Exposure by Daily Maintenance Dose† - Protocols 033, 042, 043, 044, and 058

Daily Maintenance Dose‡	Persons	Person-Time (in years)
<10 mg	22	0.30
10 to 25 mg	20	0.52
>25 mg to ≤50 mg	89	2.77
>50 mg to ≤70 mg	60	1.86
>70 mg	1	0.02

† Excludes loading dose on Day 1, if administered.
‡ Patients receiving different dosing regimens during the treatment course may appear in multiple rows

Table 15 Clinical Trial Exposure by Age Group and Gender - Protocols 033, 042, 043, 044, and 058

Age Group (years)	Person		Person-Time (in years)	
	Male	Female	Male	Female
Neonates and Newborn Infants (<28 days)	4	2	0.04	0.01
Infants & Toddlers (28 days to 23 months)	16	8	0.41	0.19
Children (2 to <12 years)	61	42	2.22	1.36
Adolescents (12 to 17 years)	23	15	1.03	0.42

Table 16 Clinical Trial Exposure by Race - Protocols 033, 042, 043, 044, and 058

Race	Persons	Person-Time (in years)
White	116	4.10
Black	13	0.37
Asian	14	0.53
American Indian or Alaska Native	12	0.26
Multiracial	16	0.42

Table 17 Clinical Trial Exposure by Ethnicity - Protocols 033, 042, 043, 044, and 058

Ethnic Origin	Persons	Person-Time (in years)
Hispanic or Latino	38	1.00
Not Hispanic or Latino	133	4.68

Table 18 Clinical Trial Exposure by Special Populations (Indications) - Protocols 033, 042, 043, 044, and 058*

Population/Indication	Persons	Person-Time (in years)
Invasive Aspergillosis	10	1.17
Esophageal Candidiasis	1	0.09
Invasive Candidiasis (including suspected cases in neonates)	56	1.54
New Onset Fever & Neutropenia (early empirical therapy)	48	1.11
Persistent Fever & Neutropenia (empirical therapy)	56	1.78

*Subjects who had hepatic impairment were excluded from clinical development

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 3.2

There are no adequate and well-controlled studies of caspofungin in pregnant or breast-feeding women. Patients who were pregnant or breast-feeding were excluded from clinical trials. In addition, patients with acute hepatitis, cirrhosis, or moderate or severe hepatic insufficiency due to any cause were excluded from all the clinical trials (adults and pediatric).

Although caspofungin has been examined in neonates and infants <3 months of age in a prospective pharmacokinetic study (Protocol 058), the safety and efficacy data for caspofungin in this age group remain limited.

SIV.1 Limitations of ADR Detection Common to Clinical Trial Development Programmes

The clinical program described in this RMP reflects exposure to caspofungin in approximately 2,900 subjects as of 01-JUN-2017, including subjects exposed for more than one year. Caspofungin was studied primarily in placebo and active-controlled trials, and in long-term follow up studies.

Common adverse reactions (incidence >1 per 100) are well characterized, as detailed in the current Summary of Product Characteristics. The sample size of the clinical development program also allowed detection of uncommon reactions (>1 per 1000). Events that may be missed include rare events (<1 per 1000), those uncommon events for which the background incidence is similar to (at least half) that of the reaction, uncommon events occurring after long-term use (>6 months), and events associated with specific concomitant diseases and/or therapy for which the clinical trials were not designed or powered to detect differences compared to controls.

The number of exposed subjects is large enough to observe possible latency (e.g., occurring more frequently over time or with delayed onset) for drug reactions of reasonable frequency (e.g., in the range of 0.5%-5%).

SIV.2 Effect of Exclusion Criteria in the Clinical Trial Development Plan

The main exclusion criteria in the clinical trial development program applicable to caspofungin are summarized in Table 19. There are no additional exclusion criteria which are not proposed to be as contraindications in the Clinical Trial Development.

Table 19 Exclusion Criteria which will Remain as Contraindications

Exclusion Criterion	Implications for Target Population
Exclusion Criterion	**Implications for Target Population**
A subject must not have a history of hypersensitivity or idiosyncratic reactions to caspofungin or another member of the echinocandin class	Do not administer to persons with known hypersensitivity to the active substance or to any of the excipients.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Pregnant and Breastfeeding Women:
There are no adequate and well-controlled studies of caspofungin in pregnant or breast-feeding women. Patients who were pregnant or breast-feeding were excluded from clinical trials.

Hepatitis and Hepatic Impairment:
Patients with acute hepatitis, cirrhosis, or moderate or severe hepatic insufficiency due to any cause were excluded from all the clinical trials (adults and pediatric).

Elderly:
There is limited treatment experience in patients 65 years of age and older (142 subjects), however no systematic dosage adjustment is required. The overall safety of caspofungin in the elderly population is similar to the adult population.

Pediatric Use:
The overall safety of caspofungin has been assessed in 171 pediatric patients who received single or multiple doses of caspofungin. The distribution among the 153 pediatric patients who were over the age of 3 months was as follows: 104 febrile, neutropenic patients; 38 patients with candidemia and/or intraabdominal abscesses, peritonitis, or pleural space infections; 1 patient with esophageal candidiasis; and 10 patients with invasive aspergillosis. The overall safety profile of caspofungin in pediatric patients is comparable to that in adult patients.

Although caspofungin has been examined in neonates and infants <3 months of age in a prospective pharmacokinetic study (Protocol 058), the safety and efficacy data for caspofungin in this age group remain limited. The ongoing clinical study, protocol 064 is currently evaluating this study population.

SIV.4 Conclusions on the Populations not Studied and Other Limitations of the Clinical Trial Development Programme

Table 20 summarizes the important identified safety concerns that have been evaluated in caspofungin RMP and do not require additional clinical trials and are evaluated through routine pharmacovigilance.

Table 20 Summary of Ongoing Safety Concerns for the Clinical Trial Program

Safety Concern	Comment	Outstanding Concern?
Increase in liver enzymes	Based on the benefit/risk assessment, current product labeling is deemed adequate to address the risk of increased liver enzymes and related events in both adult and pediatric patients at this time. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of increased liver enzymes and related events.	No
Hypersensitivity reaction including histamine-mediated allergic reactions	Based on the benefit/risk assessment, current product labeling is deemed adequate to address the risk of hypersensitivity including histamine-mediated allergic reactions in both adult and pediatric patients at this time. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of histamine-mediated allergic reactions.	No
Drug resistance	Based on the benefit/risk assessment, product labeling is deemed adequate to address the risk of drug resistance in both adult and pediatric patients at this time. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of drug resistance.	No
Drug interaction with rifampin and inducers of drug clearance	Based on the benefit/risk assessment, product labeling is deemed adequate to address the risk of drug interaction with rifampin and inducers of drug clearance in both adult and pediatric patients at this time. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of drug interaction with rifampin and inducers of drug clearance.	No
Drug interaction with cyclosporine A	Based on the benefit/risk assessment, product labeling is deemed adequate to address the risk of drug interaction with cyclosporine A in both adult and pediatric patients at this time. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of drug interaction with cyclosporine A.	No
Drug interaction with tacrolimus	Based on the benefit/risk assessment, product labeling is deemed adequate to address the risk of drug interaction with tacrolimus in both adult and pediatric patients at this time. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of drug interaction with tacrolimus.	No

Table 21 summarizes the important identified safety concerns that have been unable to be fully evaluated in caspofungin RMP and do not require additional clinical trials and are evaluated through routine pharmacovigilance.

Table 21 Safety Concerns due to Limitations of the Clinical Trial Program

Safety Concern	Comment	Outstanding Concern?
Exposure during pregnancy	Based on the benefit/risk assessment, product labeling is deemed adequate to address the risk of exposure during pregnancy to caspofungin. The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of exposure to caspofungin during pregnancy.	No
Additional data on the safety and effectiveness in neonates and infants < 3 months of age	Based on the benefit/risk assessment, product labeling is deemed adequate to address the safety and effectiveness of caspofungin in neonates and infants < 3 months of age. The actions described in the pharmacovigilance plan are deemed appropriate to address safety and effectiveness of caspofungin in neonates and infants < 3 months of age.	No

MODULE SV POST-AUTHORIZATION EXPERIENCE

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 2.0

SV.1 Action Taken by Regulatory Authorities and / or Marketing Authorization Holders for Safety Reasons

During the period covered by this RMP and cumulatively, there have been no significant actions taken by Regulatory Authorities and / or the MAH for safety reasons.

SV.2 Non-Study Post-Authorization Exposure

Market Experience

Cumulatively 26,056,068 vials have been distributed of Caspofungin acetate (as presented in Table 22 below) up to DLP of 01-Jun-2017.

SV.2.1 Method Used to Calculate Exposure

A summary of the worldwide unit distribution of caspofungin acetate for the cumulative period from market introduction to 01-Jun-2017 [a] is provided below based on the available data. Estimates of patient exposure are also provided. This estimation was based upon the following assumptions: It is assumed that each patient received one vial (50mg or 70mg) of caspofungin per day. The estimated patient-years of treatment was calculated by dividing the total number of vials distributed by 365.25 as identified in Table 22.

It is important to note that the estimated patient-years of treatment (PYT) are not equivalent to the absolute number of patients treated. It should also be noted that the overall PYT estimates are likely to underestimate the true number of patients exposed to caspofungin acetate, due to the fact that PYT estimates reflect the number of patients who could have been treated for one year based on the units distributed. However, since most patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher.

[a] The cumulative estimate of patient exposure for the reporting interval is based on the availability of monthly drug distribution figures; hence, the estimate has been calculated from market introduction to 31-May-2017, rather than through the end date of the report (01-Jun -2017).

SV.2.2 Exposure

Table 22 Post-authorization (non-study) Exposure: Units Distributed and Patient-years of Treatment, Cumulative through 0-Jun-2017

Unit Strength / Unit Size	Distribution (Number of Vials)	Exposure (Patient-years)
50mg IV	22,078,861	60,449
70mg IV	3,977,207	10,889
Total	26,056,068	71,338

SV.3 Post-Authorization Use in Populations not Studied in Clinical Trials

There are no adequate and well-controlled studies of caspofungin in pregnant or breast-feeding women. Patients who were pregnant or breast-feeding were excluded from clinical trials. In addition, patients with acute hepatitis, cirrhosis, or moderate or severe hepatic insufficiency due to any cause were excluded from all the clinical trials (adults and pediatric).

Exposure in the elderly (age 65 years and older) is collected through routine pharmacovigilance.

Reports of inadvertent exposure during pregnancy and lactation are followed through routine pharmacovigilance. Following the initial report of exposure during pregnancy, reports are followed to obtain outcome information on the pregnancy.

Exposure in patients with hepatic and renal impairment is evaluated through routine pharmacovigilance.

Based on the data available from the post-marketing environment, no new safety risks have been identified in populations not studied in clinical trials.

Caspofungin has been examined in neonates and infants <3 months of age in a prospective pharmacokinetic study (Protocol 058), additional clinical data from an ongoing study in participants < 3 months of age is pending as of this RMP update. Overall, the safety and efficacy data for caspofungin in this age group remain limited.

SV.4 Post-authorization Off-label Use

Cumulatively, there have been 103 post-marketing (non-interventional and spontaneous) reports of off-label use coded with the MedDRA preferred term of “off label use,” of which 61 (5 Serious and 56 Not Serious) have been reported in EEA.

The majority of the EEA off label uses occurred in France (n=44; 72 %); followed by UK (n=6; 10%); Spain (n=3; 5%); Italy, Poland and Belgium (each n= 2; 3 %); and Finland and Ireland (each n=; 2%) The most frequent indications for off-label use in EU are Cancidas use

in neonatal patients. A review of spontaneous reports of off label use did not reveal any further use patterns or other safety information relevant to the benefit-risk assessment for Cancidas.

SV.5 Epidemiological Study Exposure

No epidemiological safety studies have been conducted by Merck Sharp & Dohme Ltd for caspofungin acetate since the last RMP.

Exposure data for caspofungin is available from one epidemiological study (Protocol038), a retrospective chart review conducted at four sites in the United States to characterize the hepatic safety in patients receiving both caspofungin and cyclosporine A on one or more days during marketed use (P038). The data collection period was from 26-Jan-2001 to 01-Sep-2002. Forty patients receiving concomitant therapy during this time period were identified. The majority of the patients in the study were male (67.5%) and were white (70%). The median age of the study population was 47 years (range: 9 to 67 years).

The majority of patients received standard dosing regimen of caspofungin (50 mg daily, after a 70-mg loading dose on Day 1) during concomitant therapy with cyclosporine A. Two patients were pediatric patients. A PPD received a 40-mg (1.3 mg/kg) loading dose of caspofungin, followed by 30 mg (1 mg/kg) daily for a total of 54 days of caspofungin therapy. The second pediatric patient was a PPD who received 30 days of caspofungin at a loading dose of 30 mg (1.6 mg/kg), followed by 20 mg (1mg/kg) daily for 22 days. Caspofungin was then reduced to 15 mg (0.8 mg/kg) daily for 7 days.

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 2.0

SVI.1 Potential for Harm from Overdose

Higher Dose Usage of Caspofungin

This section reflects the experience of caspofungin at higher doses in a small patient subset that would have likely received higher than the labeled dose (50/70mg). The risk management plan illustrates the impact of using higher doses of caspofungin relative to the normal recommended dose of caspofungin (50 mg daily, following a 70-mg loading dose on Day 1) in adult patients.

The results of a prior Phase III study (Protocol 014) confirmed that caspofungin at a dose of 50 mg daily (following a 70-mg loading dose on Day 1) was effective and well tolerated in the treatment of adult patients with invasive candidiasis. Although the efficacy of caspofungin in this study was noninferior to amphotericin B, unfavorable responses were seen in 27% of the caspofungin-treated patients (versus 38% in the amphotericin B group), and the overall (crude) mortality in both treatment groups out to 12 weeks post-therapy was approximately 30% [Ref. 5.4: 03PH5K]. Importantly, in the more recent studies of invasive candidiasis, other antifungal agents have failed to demonstrate a significantly higher success rate or an improvement in survival relative to caspofungin at the standard 50-mg daily maintenance dose [Ref. 5.4: 03QKRL, 03PLQV, 03QKRM, 03QKRK, 03QKRN]. Therefore, the clinical practice of using higher daily maintenance doses of an echinocandin, such as caspofungin, is anticipated for a small subset of patients, specifically, those in whom the success rates in invasive candidiasis is routinely lower than 70%. For example, certain immunocompromised patient populations, such as patients with neutropenia at study entry, exhibit low success rates at the end of caspofungin (or other antifungal) therapy [Ref. 5.4: 03PH5K]. Additionally, patients with certain hard-to-manage infections, including *Candida* endocarditis, osteomyelitis, or meningitis, may require higher doses for a longer duration in an effort to exact a cure [Ref. 5.4: 03PBJD, 03QKCY]. Finally, higher doses may provide an efficacy advantage for certain difficult-to-treat infections, including those infections which are refractory to standard doses of an echinocandin or other antifungals.

In clinical trials the highest dose administered in Phase I adult studies was 210 mg, administered as a single dose to 6 healthy subjects. This dose was generally well tolerated. In addition, in the same study (Protocol 036), 100 mg once daily for 21 days has been administered to 15 healthy subjects and was generally well tolerated.

As caspofungin is a parenteral agent prepared by pharmacists predominantly in a nosocomial setting, the potential for overdose is low. Data from the completed clinical trials confirm that overdose due to caspofungin was uncommon. A total of 5 overdose reports (involving unintended doses >70 mg daily) have been received from adult clinical trials. All 5 patients received doses greater than recommended in the protocol in error. None of the patients had any adverse experiences related to the dosing errors. Two of the 5 patients were in the caspofungin invasive aspergillosis study (Protocol 019); 1 patient received caspofungin 98 mg daily for 7 days, the other 140 mg for 1 day. One patient was from the caspofungin empirical therapy study (Protocol 026) and received 200 mg of caspofungin for 1 day in error. The last two patients were in the caspofungin high-dose study (Protocol 801); both of whom received a single dose of caspofungin at 210 mg. In both cases, three 70-mg vials of caspofungin were inadvertently used to prepare the infusion instead of three caspofungin 50-mg vials of caspofungin. Both cases of overdoses occurred at the same institution; therefore, this was not a common occurrence across multiple institutions. Importantly, neither patient had an adverse experience related to the accidental overdose. The use of large, bolded lettering for the dosage strength and a different color for each dosage strength on both the vial and the carton of CANCIDAS® during marketed helps to prevent similar errors from occurring during marketed use.

In the pediatric population, a total of 2 overdose reports were received. One patient, a PPD PPD patient in the pediatric pharmacokinetic study (Protocol 042) received 2 doses of 50 mg/m daily (24 mg twice) in a single day. The second patient, a PPD patient in the pediatric empirical therapy study (Protocol 044), received a single dose of 113 mg for 1 day, followed by 80 mg daily for 10 days (instead of 70 mg daily). No adverse experience occurred in either patient.

SVI.2 Potential for Transmission of Infectious Agents

The active and inactive ingredients in CANCIDAS™ have been reviewed for conformance with the European CPMP-CVMP Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2 – Oct-2003). None of the ingredients have been identified as being of ruminant origin. No additional materials or reagents used in the preparation of the active substances, excipients, raw source materials or reagents used in the manufacturing of CANCIDAS™ are of bovine or ruminant origin.

Using validated processes, the formulated drug product is sterilized by two 0.22 µm filters in series, aseptically filled into sterile containers, and aseptically lyophilized. The sterility and *Limulus* amoebocyte lysate (LAL) endotoxin level testing performed on formal stability batches of the drug product demonstrated both sterility and unchanged levels of bacterial endotoxins.
The potential for transmission of an infectious agent has been reduced to the least possible degree.

SVI.3 Potential for Misuse for Illegal Purposes

Since caspofungin is an anti-infective agent and does not have targeted central nervous system or other direct effects on patients, the likelihood of abuse is considered to be low. Additionally, caspofungin is a parenteral agent administered by professional staff and not by patients. No evidence of drug abuse was observed in any of the caspofungin clinical trials or in the postmarketing environment.

SVI.4 Potential for Medication Errors

The potential for medication errors is considered in the following sub-sections, taking into account the common sources of medications errors. Medication Errors was recently reviewed and updated in PSUR # EMEA/H/C/PSUSA/00000576/201612 (DLP of 13-Dec-2016). In order to be consistent with the EMA Guidance to search the SMQ for Medication Errors, the MAH methodology to identifying reports suggestive of a possible medication error has been revised as of 13-JUN-2016. Note that results obtained using the search strategy implemented from 13-Jun-2016 will not be directly comparable to results reported in prior reviews of medication errors. However, the cumulative data reviewed from IBD to 01-Jun-2017 does not reflect evidence of a new concern or increase in medication errors in the EU which warrants additional risk minimization efforts at this time.

SVI.4.1 Description of Medication Errors During the Clinical Trial Programme

Experience in Clinical Trials: Of the 1193 adult patients included in the completed Phase II/III trials, a total of 8 (0.7%) patients had one or more reported dosing/administration errors. Most were minor deviations, and no adverse experiences were reported as a result of these dosing errors. A description of the errors in these 8 patients follows:

- AN PPD (Protocol 007) received ~40 mg of caspofungin daily even though the patient was enrolled into the caspofungin 50 mg group.
- AN PPD (Protocol 007) received ~64 mg of caspofungin on Day 1, rather than the 70-mg loading dose in Day 1. This was due to study drug preparation error.
- AN PPD (Protocol 019) received caspofungin 50 mg daily for 3 days, 78 mg for 1 day, and 98 mg for 1 day even though the patient was enrolled into the caspofungin 70 mg group.
- AN PPD (Protocol 019) received caspofungin 50 mg daily for 2 days and 140 mg for 1 day (instead of the prescribed 70 mg daily dose).
- AN PPD (Protocol 019) received caspofungin 70 mg for 2 days (instead of the prescribed 100 mg daily dose).
- AN PPD (Protocol 019) received 50 mg for 1 day in error (instead of the prescribed 100 mg daily dose).

- AN PPD (Protocol 801) received 210 mg for 1 day in error (instead of the prescribed 150 mg daily dose).
- AN PPD (Protocol 801) received 210 mg for 1 day in error (instead of the prescribed 150 mg daily dose).

Of the 171 pediatric patients included in the Phase II trials, a total of 2 (1.2%) patients had one or more dosing/administration errors reported. No adverse experiences were reported as a result of these dosing errors. A description of the errors in these 2 patients as follows:

- AN PPD (Protocol 042) erroneously received 2 separate doses of caspofungin on the same day (each at a 24-mg dose). This resulted in an unintentional study drug overdose on that day.
- AN PPD (Protocol 044) received caspofungin at 113 mg daily instead of the prescribed 70-mg maximum daily dose.

Table 23 Description of Medication Errors During the Clinical Trial Programme

Description of Medication Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
Wrong Dose	10	Study site personnel did not follow instructions for dispensing study medication.	Clear and specific instructions for dispensing study medication were provided to study site personnel.	See above text for additional details

SVI.4.2 Preventive Measures for the Final Product(s) Being Marketed

No safety issues have been identified with respect to medication errors in the clinical trial programme. Based on the available clinical trial data, no specific preventive measures are deemed necessary. The SmPC provides information to the healthcare provider on the appropriate use, administration, and storage of CANCIDAS®. Though there have been no medication errors of significance reported and no safety issues identified regarding medication errors in any of the clinical studies for CANCIDAS®, the MAH has been proactive in implementing preventative measures to reduce the potential for medication errors in the post-marketing environment.

Prevention of Error due to Wrong Medication Administered: Strict country specific regulatory guidelines are followed regarding brand and generic name placement and prominence on cartons and vials. Per regulatory guidelines, drugs list brand names prominently and in bold letters, compared to the generic name, on each carton and vial. To prevent errors in prescribing and dispensing, the vials are individually, clearly labeled as CANCIDAS® (caspofungin acetate) in either a 50-mg or a 70-mg dose. The labels measure 2 3/4" by 15/16" and are clearly marked with the appropriate dose in white on

pantone 202 color. The vials are also clearly labeled "for intravenous use after reconstitution and dilution". The labels provide clear visual differentiation from other currently marketed echinocandins, thus minimizing the risk of medication errors. The drug is provided in individual vials that are then individually packaged in a carton which are also individually clearly labeled as CANCIDAS® (caspofungin acetate) in either a 50 mg or a 70 mg dose.

Prevention of Error due to Inappropriate Dose and Schedule of Administration: The SmPC provides clear and concise information regarding the age, dose and the schedule for vaccination within the sections for *Therapeutic indications* and *Posology and method of administration,* respectively. Each carton contains an insert that provides information to the health care provider and consumer on the appropriate use of the medication. Instructions for the preparation, dosing, and use of CANCIDAS® in pediatric patients are provided in the product label (SmPC), including information on how to calculate body surface area to determine proper dosing.

Prevention of Error due to Incorrect Route of Administration: The labeling information within the SmPC clearly specifies that the drug is to be injected intravenously.

Prevention of Error due to Incorrect Storage: To minimize the risk of incorrect storage, the SmPC contains clear information regarding the appropriate storage conditions for CANCIDAS®. Additionally, the cartons and single-dose vials are individually and clearly labeled and marked with the appropriate storage requirements for CANCIDAS®.

In summary, the MAH has proactively implemented preventative measures to reduce the overall number of medication errors, and to prevent specific errors in prescribing, dispensing, administration and storage of CANCIDAS® in the post-marketing environment No additional specific preventive measures are deemed necessary.

SVI.4.3 Effect of Device Failure

Not applicable, as this product does not involve a medical device.

SVI.4.4 Reports of Medication Errors with the Marketed Product(s)

In order to be consistent with the EMA Guidance to search the SMQ for Medication Errors, the MAH methodology to identifying reports suggestive of a possible medication error has been revised as of 13-JUN-2016. The methods utilized and results obtained using the search strategy implemented and utilized in this RMP as well as PSUR # EMEA/H/C/PSUSA/00000576/201612, will not be directly comparable to results reported in prior reviews of medication errors.

Postmarketing Experience: Cumulatively, there have been 257 (32 Serious and 225 Non-Serious) reports of medication errors or potential prescription/medication errors have been identified since IBD through 01-Jun-2017. The majority of the reports were of drug administration error (e.g. intravenous push) (69), product preparation error (49) improper storage (e.g. product not refrigerated) (19), inappropriate schedule of drug administration

(12), incorrect route of drug administration (12) and wrong technique in product usage process (11). The remaining reports concerned a variety of other medication errors that were singly reported (i.e. vial strongly shaken, diluted in vancomycin, heparin infused in same device, wrong patient given drug, received drug from recalled lot, medication not administered due to medication noncompliance or loss of intravenous access and dose administered after caspofungin discontinued). All medication error terms with number of occurrences presented in the Table 24 below. A review of the 257 cumulative reports demonstrated 183 cases (71%) with no AE Preferred Terms coded outside of Medication Error SMQ. The remaining 74 reports were indicative of the underlying and/or treated medical conditions, where Cancidas was prescribed in medically complex patients with underlying confounding medical conditions and concomitant medications. Several cases (14=5.4%) reported local reaction (such as erythema and swelling) following perivascular injection or administration of caspofungin into soft tissue as well as topical exposure to caspofungin and the development of itching, erythema, and a hypersensitivity reaction. The majority of these cases contained limited clinical information beyond the PTs reported. The remaining adverse events suggested no sequelae of the medication error, and all were consistent with indication for use or concurrent conditions.

In summary, no specific pattern of medication error was identified that could indicate a particular safety risk. Product labeling for caspofungin includes information regarding appropriate indication, dosage schedule, reconstitution, and storage.

Table 24 Description of Medication Errors with the Marketed Product

Description of Medication Error	Percentage of Medication Error Events)	Analysis of Cause	Steps Taken to Prevent	Comment
Drug administration error	~49%	Human error on administration by the HCP. Regarding the general term of drug administration error, this preferred term is a general term reflecting a number of different types of errors. In many of these reports, the term drug administration error was coded instead of a more specific available MedDRA medication error term. Review of the overall number and type of drug administration error reports did not reveal any significant pattern.	See text above under "Preventive Measures for the Final Product(s) Being Marketed) Br comment regarding preventative measures for specific types of medication error. No further preventative measures are necessary.	No pattern of safety concern identified. The majority of reports do not have associated AEs. Of those that do, most are non-serious and/or listed and/or consistent with the known safety profile in general and/or the target population for CANCIDAS®.
Medication error	~24%	Human error related to administration by the HCP. Regarding the general term of medication error, this preferred term is a general term reflecting a number of different types of errors. In many of these reports, the term "medication error" was coded instead of a more specific available MedDRA medication error term. Review of the overall number and type of medication error reports did not reveal any significant pattern.	See text above under "Preventive Measures for the Final Product(s) Being Marketed" for comment regarding preventative measures for specific types of medication error. No further preventative measures are necessary.	No pattern of safety concern identified. The majority of reports do not have associated AEs. Of those that do, most are non-serious and/or listed and/or consistent with the known safety profile in general and/or the target population for CANCIDAS®.
Product preparation error	~19%	Human error on administration by the HCP. Review of the overall number and type of product preparation error reports did not reveal any significant pattern.	See text above under "Preventive Measures for the Final Product(s) Being Marketed" for comment regarding preventative measures for specific types of medication error. No further preventative measures are necessary.	No pattern of safety concern identified. The majority of reports do not have associated AEs. Of those that do, most are non-serious and/or listed and/or consistent with the known safety profile in general and/or the target population for CANCIDAS®.

Table 24 Description of Medication Errors with the Marketed Product

Description of Medication Error	Percentage of Medication Error Events)	Analysis of Cause	Steps Taken to Prevent	Comment
Incorrect product storage	~7%	Reports typically are received from HCPs when functionality issues with the storage unit are discovered by site personnel.	See text above under "Preventive Measures for the Final Product(s) Being Marketed" for comment regarding preventative measures for specific types of medication error. No further preventative measures are necessary.	No pattern of safety concern identified. The majority of reports do not have associated AEs. Of those that do, most are non-serious and/or listed and/or consistent with the known safety profile in general and/or the target population for CANCIDAS®.
Incorrect route of drug administration	~5%	Human error associated with administration by the HCP. All cases reflected an alternative route of administration rather than intravenous.	See text above under "Preventive Measures for the Final Product(s) Being Marketed" for comment regarding preventative measures for specific types of medication error. No further preventative measures are necessary.	No pattern of safety concern identified. The majority of reports do not have associated AEs. Of those that do, most are non-serious and/or listed and/or consistent with the known safety profile in general and/or the target population for CANCIDAS®.
Expired product administered	~2%	Human error discovered after administration of the product.	Expiry date is printed on the product packaging and on the vial. Specific and clear information is also provided in Company Core Date Sheet (CCDS) regarding shelf life of CANCIDAS®.	No pattern of safety concern identified

SVI.5 Potential for Off-Label Use

Off-label use by health care professionals is a possibility with any marketed product. Health care professionals could potentially prescribe caspofungin in adult patients for the following reasons: (1) the treatment of fungal infections for which caspofungin is not approved (i.e., non-Aspergillus mold or non-Candida yeast infections); (2) antifungal prophylaxis to prevent the development of fungal infections in high-risk patient populations; (3) use in combination of other antifungals for the treatment of fungal infections for which caspofungin is or is not indicated in the Product Circular; (4) use of higher-than-approved doses of caspofungin.

SVI.6 Specific Pediatric Issues

Caspofungin clinical trials experience includes pediatric participants (3 months to 17 years of age). The overall safety of caspofungin was assessed in 171 pediatric patients who received single or multiple doses of caspofungin. Among the 153 pediatric patients who were over the age of 3 months, there were104 febrile, neutropenic patients; 38 patients with candidemia and/or intraabdominal abscesses, peritonitis, or pleural space infections; 1 patient with esophageal candidiasis; and 10 patients with invasive aspergillosis.

The overall safety profile of caspofungin in pediatric patients is generally comparable to that in adult patients.

SVI.6.1 Issues identified in Pediatric Investigation Plans

The efficacy and safety of caspofungin has not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age. Although limited pharmacokinetic data were collected in neonates and infants below 3 months of age, these data are insufficient to establish a safe and effective dose of caspofungin in the treatment of neonatal candidiasis. Invasive candidiasis in neonates has a higher rate of CNS and multi-organ involvement than in older patients; the ability of caspofungin to penetrate the blood-brain barrier and to treat patients with meningitis and endocarditis is unknown. Caspofungin has not been studied in pediatric patients with endocarditis, osteomyelitis, and meningitis due to *Candida*. Caspofungin has also not been studied as initial therapy for invasive aspergillosis in pediatric patients. There are no current pending or planned long term follow up of safety or efficacy issues in related to the pediatric use of this product. There is currently one ongoing clinical study evaluating caspofungin vs. amphotericin B in subjects < 3 months of age in subjects with invasive candidiasis. At the completion of this study the clinical development program for caspofungin will conclude.

SVI.6.2 Potential for pediatric off-label use

CANCIDAS® is indicated in patients >12 months of age. The safety and efficacy of CANCIDAS® in children <12 months of age have not been established and CANCIDAS® is not indicated in this subset of the pediatric population. The age groups studied in the clinical trials along with immunogenicity and safety data for the ages indicated is clearly stated in the SmPC.

SVI.7 Conclusions

Table 25 Safety Concerns from Module SVI (Additional EU Requirements for the Safety Specification)

Safety Concern	Comment
None	N/A

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 3.2

SVII.1 Newly Identified Safety Concerns

During routine safety surveillance, reports of SJS and TEN were identified for review. To assess whether there was a signal of SJS and TEN, a literature review and case-level evaluation of postmarketing adverse event reports were performed. The Merck safety database was queried for all post-marketing reports of Serious Cutaneous Adverse Reactions (SCARs) received from healthcare providers in temporal association with the administration of caspofungin acetate during the period from market launch (14-DEC-2000) through 23-SEP-2015 using the narrow SMQ for SCARs.

Forty-two reports were identified within the narrow SMQ of SCAR (37 serious and 5 non serious), 41 were spontaneous reports and 1 from a non-interventional study. Of the 42 identified reports, 31 were received from the EU (24 from France), 4 from the United States, and 7 from the Rest of World. Of the 42 reports, 20 occurred in females and 22 in males with an age range at the time of the event between 13 years and 86 years, and average age of 53 years. The time to onset (TTO) from the earliest therapy start date was known in 33 of the 42 reports; TTO ranged from 1 to 43 days with an average TTO of 13 days. Outcome was reported for 38 of the 42 cases. Of these 38 cases with reported outcomes, 27 were reported to have recovered/recovering; 6 were reported to have not recovered; and 5 events were reported as fatal. Of these 38 cases, 8 were SJS cases. Out of 8 cases, 4 cases were confounded by concomitant medications, 3 had limited information and 1 case had a positive dechallenge. There were 9 cases of TEN of which 5 cases were confounded by concomitant medications, 2 with no temporal relationship to caspofungin acetate, 1 with limited information and 1 with a positive dechallenge and rechallenge. Based on this evaluation, SJS and TEN have been added to the CCDS. The addition of these very rare events does not alter the favorable benefit/risk profile of caspofungin.

Additional cases of SJS/TEN have been received after the datalock point of the initial signal evaluation and are discussed in Table 26 for completeness. These cases were similar to those identified in the initial signal evaluation and did not highlight any additional safety concerns. Since the newly identified serious skin reactions of SJS/TEN are considered severe forms of hypersensitivity reactions, the important identified risk of histamine-mediated allergic reactions has been broadened to be the important identified risk of hypersensitivity, and now includes histamine-mediated allergic reactions and SJS/TEN.

Table 26 Newly Identified Safety Concern(s)

Important Identified Risk: **SJS/TEN**
Details: Reports of SJS and TEN were identified during routine safety surveillance
Source: Post marketing spontaneous and literature cases
New studies proposed in pharmacovigilance plan? No
New risk minimization actions proposed? No

SVII.2 Recent Study Reports with Implications for Safety Concerns (non-ATMP products)

Not Applicable

SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-Authorization Experience

Table 27 Details of Important Identified Risk: Increase in liver enzymes

Frequency with 95%CI	***Adult Phase II/III Studies*** Increased ALT*: 84/1178 (7.1%) 95% CI = (5.7, 8.8) Increased AST*: 78/1172 (6.7%) 95% CI = (5.3, 8.2) *Increased ALT and AST were those increases considered by the investigator to be an adverse event and at least possibly related to therapy with caspofungin.	Pediatric Studies Increased ALT*: 11/170 (6.5%) 95% CI = (3.3, 11.3) Increased AST*: 13/170 (7.6%) 95% CI = (4.1, 12.7) *Increased ALT and AST were those increases considered by the investigator to be an adverse event and at least possibly related to therapy with caspofungin.
Seriousness / Outcomes	***Adult Phase II/III Studies*** ALT and AST laboratory data were available from 1178 and 1172 caspofungin-treated patients, respectively. A total of 126 patients experienced a laboratory adverse event of (any) ALT increase (84/1178; 7.1%) and/or (any) AST increase (78/1172; 6.7%) that were considered by the investigator to be at least possibly related to caspofungin therapy. None of the laboratory adverse events were considered to be serious by the investigator. Notably, there were no clinical adverse events associated with the hepatic enzyme elevations. Three of the patients (~2.5%) with increases in AST and/or ALT discontinued caspofungin therapy as a result of the laboratory adverse event.	***Pediatric Studies*** ALT and AST laboratory data were available from 170 pediatric patients treated with caspofungin that had follow-up laboratory data collected. A total of 15 pediatric patients experienced a laboratory event of (any) ALT increase (11/170; 6.5%) and/or (any) AST increase (13/170; 7.6%) that were considered by the investigator to be at least possibly related to caspofungin therapy. None of the laboratory adverse events were considered to be serious by the investigator, and none of the patients with increase in AST/ALT discontinued caspofungin therapy as a result of the laboratory adverse event. Notably, there were no clinical adverse events associated with hepatic enzyme elevations.

Table 27 Details of Important Identified Risk: Increase in liver enzymes

	Following discontinuation, the liver enzyme(s) remained mildly elevated (<2x ULN) in two of these patients, and decreased to within 2x ULN in the third patient. As demonstrated by the high-dose study (Protocol 801), the incidence of ALT increase and/or AST increase in patients who received caspofungin at 150 mg daily was similar to those patients who received caspofungin at the approved 50 mg daily dose (following a 70-mg loading dose on Day 1). **Postmarketing Data** Through 01-Jun2-017, 487 cases (752 events) were received for the adult population or with no reported age of the patient, for the Liver related investigations, signs and symptoms (Standard MedDRA Query (SMQ) – Broad). Of the 487 cases, 294 were spontaneously reported and 193 were received through the non-interventional studies. Two hundred and twenty seven (227) cases were reported as serious and 260 as non- serious. Ninety four (94) cases were received from the United States, 133 from EU and 260 from the rest of the world. The median age was 59 years of age with the minimum of 18 years of age and the maximum of 87 years of age. The time to onset (TTO) was reported in 334 cases (520 events). The median TTO was reported as 8 days with the minimum of 1 day and the maximum of 377 days. The most common (≥5) serious preferred terms (PT) reported for this SMQ were the following: Aspartate aminotransferase (AST) increased n= 56; Blood alkaline phosphatase increased n=56; Alanine aminotransferase increased (ALT) n=55; Hepatic function abnormal n=37; Blood	**Postmarketing Data** In the pediatric population, through 01-Jun-2017, total of 49 cases (87 events) were reported for the Liver related investigations, signs and symptoms (Standard MedDRA Query (SMQ) – Broad). Of the 49 cases, 26 were spontaneously reported and 23 were received through the non-interventional studies. Thirty (30) cases were reported as serious and 19 as not serious. Eleven (11) cases were received from the United States, 14 from EU and 24 from the rest of the world. The median age was 9 years of age with the minimum of 1.5 months of age and the maximum of 17 years of age. The time to onset (TTO) was reported in 38 cases (62 events). The median TTO was reported as 8 days with the minimum of 1 day and the maximum of 154 days. The most common (≥5) serious PTs reported for this SMQ were: Alanine aminotransferase increased n=19; Aspartate aminotransferase increased n=14; Gamma-glutamyltransferase increased n=12; Hepatic function abnormal n=9; Blood alkaline phosphatase increased n=7; Blood bilirubin increased n=7; Transaminases increased n=5. Eleven (11) cases reported fatal outcome. Of these 11 cases, 1 case included hepatic events that were assessed as being fatal, the remainder of the fatal cases included hepatic events that either recovered or outcome was not provided. All fatal cases described critically ill patients who experienced hepatic events which were likely manifestation of their primary disease, confounded by underlying medical conditions and multiple concomitant medications. Twenty eight (28) cases reported outcome as recovered/recovering, 8 as not recovered and 2 of the cases reported the outcome as unknown.

Table 27 Details of Important Identified Risk: Increase in liver enzymes

	bilirubin increased n=35; Gamma-glutamyltransferase (GGT) increased n=28; Hepatic enzyme increased n=25; Hyperbilirubinaemia n=17; Transaminases increased n=16; Liver function test (LFT) abnormal n=15; LFT increased n=10 Eighty nine (89) cases reported fatal outcome. Of these 89 cases, 17 cases included hepatic events that were assessed as being fatal, the remainder of the fatal cases included hepatic events that either recovered or outcome was not provided. Of the 89 fatal cases, 22 provided limited information and the remaining 67 cases described critically ill patients who experienced hepatic events which were likely manifestation of their primary disease, confounded by underlying medical conditions, or confounded by concomitant medications. Two hundred and sixty (260) cases reported outcome as recovered/recovering, 99 as not recovered and the rest of the cases reported the outcome as unknown.	
Severity and Nature of the Risk	***Adult Phase II/III Studies*** *Severity:* Asymptomatic elevations in AST and/or ALT were observed in the Phase II/III clinical trials involving adults. Most AST and/or ALT increases were reversible and of mild intensity (<5 x ULN). Many had returned to normal and/or were trending downward with continued caspofungin therapy or during the post-therapy follow-up period. *Nature of Risk*: The fundamental concern of ALT/AST elevations is that these events are a potential harbinger of significant liver injury, which could then lead to the development of serious, permanent dysfunction (i.e., hepatic insufficiency or failure) or parenchymal changes in the liver (i.e., hepatic necrosis). However, the	***Pediatric Studies*** *Severity:* Asymptomatic elevations in AST and/or ALT were observed in the clinical trials involving pediatric patients. Most AST and/or ALT increases were reversible and of mild intensity (<5 x ULN). Many had returned to normal and/or were trending downward with continued caspofungin therapy or during the post- therapy follow-up period. *Nature of Risk*: There is the same fundamental concern of ALT/AST elevations in pediatric patients as described in adult patients. Notably, the ALT or AST elevations seen in the pediatric trials were predominantly reversible findings, and none were associated with clinical sequelae. There also is no signal of clinical hepatotoxicity in pediatric patients

Table 27 Details of Important Identified Risk: Increase in liver enzymes

	ALT or AST elevations seen in the adult trials were predominantly reversible findings, and none were associated with irreversible clinical sequelae. There also is no signal of clinical hepatotoxicity in adult patients treated with caspofungin from post-marketing experience as described below under Postmarketing Data.	treated with caspofungin from postmarketing experience as described below under Postmarketing Data.
Background Incidence / Prevalence	The target population would be treated with another antifungal if not treated with caspofungin. Thus, background rates in the population are considered to be rates in those treated with other antifungal agents. Hepatic effects (elevated ALT and/or AST) have been noted during treatment with other antifungal agents with the following frequencies: <u>Increased ALT</u>: ▪ 8.1% - 14.1 % with amphotericin B [Ref. 5.4: 03QG04, 03PH5K] • 14.6% with liposomal amphotericin (AmBisome™) [Ref. 5.4: 03PH5K] <u>Increased AST</u>: ▪ 9.0% - 12.8% with amphotericin B [Ref. 5.4: 03QG04, 03PH5K] • 12.8% with AmBisome™ [Ref. 5.4: 03PH5K] <u>Any liver enzyme elevation</u>: • 10% with amphotericin B [Ref. 5.4: 03QG04] and 14% with fluconazole [Ref. 5.4: 03P4R0] Note that different definitions may have been used to define increased ALT, AST or any liver enzyme elevation. For amphotericin B [Ref. 5.4: 03QG04], increased ALT and increased AST or any liver enzyme elevation were those increases considered by the investigator to be an adverse event and at least possibly related to study therapy. For data abstracted from the AmBisome™ label for amphotericin B and AmBisome™ [Ref. 5.4: 03PH5K], increased ALT and increased AST were reported as common adverse events (incidence of 10% or greater), regardless of relationship to study drug. Liver enzyme elevations were not defined in the reference for fluconazole [Ref. 5.4: 03P4R0].	
Risk Groups or Risk Factors	The risk factors associated with the development of aminotransferase (ALT or AST) elevations in both adult and pediatric patients are multifactorial in nature. Particularly, patients at risk for development of an invasive fungal infection have a variety of risk factors that could predispose towards the development of such elevations, including the underlying fungal infection (e.g., hepatic involvement of liver with candidiasis), the underlying medical conditions (e.g., hypotensive shock due to sepsis, venoocclusive disease, hepatic graft-versus-host disease), or concomitant medications (e.g., cytotoxic chemotherapy for the treatment of underlying malignancy; fluoroquinolones, cephalosporins, or other antimicrobial therapy; triazoles). The development of transaminase elevations in patients receiving caspofungin could be impacted by anyone or a multiple number of these risk factors. Theoretically, preexisting elevations in ALT or AST could also predispose the patient towards the development of further increases upon initiation of caspofungin therapy. However, this is not proven, and countered by the fact that similar elevations in AST/ALT have been seen in the Phase I healthy volunteer studies.	

Table 27 Details of Important Identified Risk: Increase in liver enzymes

	Notably, concomitant use of caspofungin with cyclosporine A has been identified as a unique risk factor in patients and healthy volunteers. Some healthy volunteers who received two 3 mg/kg doses of cyclosporine A with caspofungin showed transient increases in alanine transaminase (ALT) and aspartate transaminase (AST) of less than or equal to 3-fold the upper limit of normal (ULN) that resolved with discontinuation of the treatment. However, in a retrospective study of 40 patients treated during marketed use with CANCIDAS®; and cyclosporine A for 1 to 290 days (median 17.5 days), no serious hepatic adverse events were noted.		
Potential Mechanisms	The potential mechanism for aminotransferase elevation with caspofungin use is unknown. There were no effects on transaminase values in rats administered caspofungin for up to 27 weeks in the preclinical toxicology studies. However, very slight (approximately 2-3 fold) increases in transaminase values have occurred in monkeys administered caspofungin in the preclinical toxicology studies. Notably, the transaminase values did not increase further despite continued treatment of up to 27 weeks duration. There were no consistent histopathologic changes that correlated with these increases in transaminase values (scattered foci of subcapsular necrosis occurred in some animals in a 5-week study; however, no histopathologic changes occurred in a 27-week study at higher doses).		
Preventability	There are no clear measures to prevent the elevations in liver function tests following the administration of caspofungin. Specifically, patients receiving concomitant caspofungin and cyclosporine A should have close monitoring of liver enzymes as described in Section 4.4 of SmPC. In all other patients who develop transaminase elevations while on caspofungin therapy, consideration should be given towards monitoring for a worsening in transaminase elevations or the development of clinical evidence of hepatic dysfunction. In the event of these events, the patients should be evaluated for the risk/benefit of continuing caspofungin therapy as described in Section 4.4 of SmPC.		
Impact on the Individual Patient	The majority of patients who experience increase in liver enzymes have mild to no symptoms and recover with no complications or sequela.		
Potential Public Health Impact of Safety Concern	Severe (Grade 3 or 4) liver enzyme elevations may on occasion be associated with acute liver failure. Generally, however, elevations are transient and not associated with clinical sequelae. Notably, liver enzyme levels may vary with many cofactors, such as high-fat meals, ethanol use, and co-morbidities with concomitantly prescribed medications. There is no signal of clinical hepatotoxicity associated with the generally mild and transient liver enzyme elevations seen with caspofungin use in clinical trials.		
Evidence Source	***Adult Phase II/III Studies***	***Pediatric Studies***	***Post-marketing data***
MedDRA Terms	*Clinical Terms* 1. Alanine Aminotransferase (ALT) increase 2. Aspartate Aminotransferase (AST) increase *Post-marketing Term:* Standard MedDRA Query (SMQ) Liver related investigations, signs and symptoms(Standard MedDRA Query – Broad)		

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

Frequency with 95%CI	***Adult Phase II/III Studies*** *Clinical Adverse Experiences:* Any Histamine-mediated Allergic Reaction 58/1193 (4.9%) 95% CI = (3.7, 6.2) *Laboratory Adverse Experiences:* Eosinophil Count Increased 12/1144 (1%) 95% CI = (0.5, 1.8)	***Pediatric Studies*** *Clinical Adverse Experiences:* Any Histamine-mediated Allergic Reaction 7/171 (4.1%) 95% CI = (1.7, 8.3) *Laboratory Adverse Experiences:* Eosinophil Count Increased 2/167 (1.2%) 95% CI = (0.2, 4.3)
Seriousness / Outcomes	***Adult Phase II/III Studies*** *Clinical Adverse Experiences*: Fifty-eight of the 1193 patients (4.9%) who received caspofungin in the adult Phase II/III studies had at least 1 of the aforementioned clinical adverse experiences which were considered to be at least possibly related to caspofungin therapy. Of those, 2 (0.2%) led to the discontinuation of therapy. Only 1 (0.1%) was deemed serious by the investigator; this event also led to discontinuation of therapy. This patient experienced hypersensitivity, manifested by chills, severe rigors, chest tightness, and tachypnea, on the first day within 15 minutes of the start of the caspofungin infusion. The symptoms diminished after caspofungin was discontinued. Additionally, 1 patient from the Caspofungin Compassionate Use study (Protocol 024/025) experienced an anaphylactic reaction during infusion on Day 1 of therapy. Caspofungin treatment was discontinued and symptoms resolved within 15 minutes after administration of IV diphenhydramine and hydrocortisone. The remaining clinical adverse experiences related to histamine-mediated reactions all occurred in less than 2% of the caspofungin-treated patients: bronchospasm (0.1%), wheezing 0.2%), erythema (0.7%), face oedema (0.1%), pruritus (1.2%), generalized pruritus (0.2%),	***Pediatric Studies*** *Clinical Adverse Experiences*: Seven of the 171 patients (4.1%) who received caspofungin in the pediatric clinical studies had at least 1 of the aforementioned clinical adverse experiences which were considered to be at least possibly related to caspofungin therapy. None of these adverse experiences were deemed serious by the investigator. Only 1 (0.6%) of the patients experienced an interruption of caspofungin therapy, and none of the events led to caspofungin discontinuation. The breakdown of clinical adverse experiences related to histamine-mediated reactions is as follows: pruritus (1.8%), urticaria (0.6%), flushing (1.8%), and erythema (0.6%). All of the reported events resolved by the end of the study. None of the pediatric patients had any of the other aforementioned clinical adverse experiences related to histamine- mediated reactions. No cases of SJS/TEN were seen during clinical trials. *Laboratory Adverse Experiences*: Eosinophil laboratory data were available from 167 caspofungin-treated patients. Two (1.2%) developed a drug-related increase in the eosinophil count that was considered to be at least probably related to caspofungin therapy. None of these cases were deemed serious by the investigator and none led to discontinuation of caspofungin therapy.

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

	erythematous rash (0.3%), pruritic rash (0.3%), facial swelling (0.2%), urticaria (0.4%), and flushing (1.3%). No cases of SJS/TEN were seen during clinical trials. Most of these events were transient; all but 3 (2 pruritus, 1 erythema) resolved by the end of the study. As demonstrated by the high-dose study (Protocol 801), there was no notable difference in the incidence of histamine-mediated reactions between those patients who received caspofungin at 50 mg daily (following a 70-mg loading dose on Day 1) and those who received caspofungin at 150 mg daily. *Laboratory Adverse Experiences:* Eosinophil laboratory data were available from 1144 patients treated with caspofungin. Twelve (1.0%) developed a drug-related increase in the eosinophil count that was considered to be at least possibly related to caspofungin therapy. None of these cases were deemed serious by the investigator and none led to discontinuation of caspofungin therapy. Most patients who experienced elevations in eosinophil values had normalization of these values by the completion of the study. **Postmarketing Data** Through 01Jun2017,, 191 cases (209 events) were received for the adult population or with no reported age of the patient for the Histamine-mediated allergic reactions (excluding SJS/TEN). The preferred terms were distributed as below (N= events): Rash N=110; Erythema N= 30; Pruritus N=22; Hypersensitivity N=16; Urticaria N=16; Anaphylactic reaction N=9; Face oedema N= 4; Rash pruritic N=2.	**Postmarketing Data** Through 01Jun2017,, 14 cases (19 events) were received for the pediatric population for the Histamine-mediated allergic reactions (excluding SJS/TEN). The preferred terms were distributed as below (N= events): Rash N=4; Erythema N= 1; Pruritus N=4; Hypersensitivity N=1; Urticaria N=2; Anaphylactic reaction N=3; Face oedema N= 2; Rash pruritic N=1; Local swelling N=1. Of 14 cases, 13 were spontaneously reported and 1 was received through the non-interventional study. Seven (7) cases were reported as serious and 7 as not serious. One (1) case was received from the United States, 7 from the EU and 6 from the rest of the world. The median age was 7 years old with the minimum of 1.5 years old and the maximum of 15 years old. One (1) case (0.02%) reported fatal outcome. The case was confounded by patient's underlying conditions, multiple comorbidities and concomitant medications. Two (2) cases reported outcome as not recovered, 7 as recovered/recovering and the rest of the cases reported the outcome as unknown. The time to onset (TTO) was reported in 10 cases (13 events). The median TTO was reported as 2 days with the minimum of 1 day and the maximum of 114 days. Additionally, 3 cases (3 events) have reported Preferred terms of SJS/TEN in pediatric population. All cases were spontaneous and reported as serious. Two (2) events were reported for the SJS and 1 for the TEN.

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

	Of 191 cases, 164 were spontaneously reported and 27 were received through the non-interventional studies. Seventy (70) cases were reported as serious and 139 as not serious. Forty nine (49) cases were received from the United States, 73 from EU and 69 from the rest of the world. The median age was 60 years old with the minimum of 18 years old and the maximum of 89years old. Six (6) cases reported fatal outcome. Of these 6 cases, 2 cases included histamine-mediated allergic reaction events that were assessed as being fatal, the remainder of the fatal cases included hepatic events that either recovered or outcome was not provided. Of 6 fatal cases, 1 case contained limited information The remaining fatal cases were confounded by underlying medical conditions and concomitant medications. Nine (9) cases reported outcome as not recovered, 117 as recovered/recovering and the rest of the cases reported the outcome as unknown. The time to onset (TTO) was reported in 122 cases (137 events). The median TTO was reported as 3 days with the minimum of 1 day and the maximum of 146 days. <u>SJS/TEN:</u> Additionally, 18 cases (19 events) have reported PT terms of SJS and/or TEN All cases were spontaneous and reported as serious. Nine (9) events were reported for the SJS and 10 for the TEN. Of these 18 cases, 3 cases reported a positive dechallenge and one case reported a positive dechallenge/rechallenge to caspofungin. The remaining 15 cases were confounded by concomitant medications and/or patient's underlying conditions.	One (1) case was reported from the United States, 1 from the EU and 1 from Spain. The median age was reported as 15 years old with the minimum of 3years old and the maximum of 17years old. One (1) case reported fatal outcome and 2 cases reported outcome as recovered/recovering. The time to onset (TTO) was reported in 2 cases (2 events). The median TTO was reported as 10.5 days with the minimum of 2 days and the maximum of 19 days. <u>SJS/TEN</u> Additionally, 3 cases (3 events) have reported Preferred terms of SJS/TEN in pediatric population. All cases were spontaneous and reported as serious. Two (2) events were reported for the SJS and 1 for the TEN. Two (2) out of 3 cases reported a positive dechallenge to caspofungin. One (1) case was reported from the United States, 1 from the EU and 1 from Spain. The median age was reported as 15 with the minimum of 3 and the maximum of 17. One (1) case reported fatal outcome and 2 cases reported outcome as recovered/recovering. The fatal case reported critically ill patient and was confounded by patient's underlying condition as well as concomitant medications, however a positive dechallenge was noted. The time to onset (TTO) was reported in 2 cases (2 events). The median TTO was reported as 10.5 days with the minimum of 2 days and the maximum of 19 days.

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

	Four (4) cases were reported from the United States, 11 from the EU and 3 from the rest of the world. The median age was reported as 57 years with the minimum of 21years and the maximum of 86 years. Eight (8) cases reported fatal outcome. Four (4) cases reported outcome as not recovered, 4 as recovered/recovering and 2 of the cases reported the outcome as unknown. All fatal cases either contained limited information and/or were confounded by concurrent conditions and/or concomitant medications. The time to onset (TTO) was reported in 12 cases (12 events). The median TTO was reported as 9 days with the minimum of 2 days and the maximum of 23 days.	
Severity and Nature of the Risk	***Adult Phase II/III Studies*** *Severity:* Two serious adverse events (hypersensitivity and anaphylaxis) related to histamine-mediated reactions were reported. The majority of the histamine-mediated adverse events were mild or moderate; less than 10 events were of severe intensity. Very few histamine-mediated adverse events (0.2%) led to discontinuation of caspofungin therapy. *Nature of Risk:* The major concerns of histamine-mediated events include the potential that these events could lead to significant and potentially fatal respiratory or cardiovascular compromise, or to permanent clinical sequelae (i.e., irreversible skin or lung damage). All respiratory findings (i.e., hypersensitivity, bronchospasm, anaphylaxis, wheezing) were reversible. None led to any clinical sequelae, and all but 3 events (2 pruritus, 1 erythema) had resolved by the end of the study.	***Pediatric Studies*** *Severity:* None of the adverse events listed above were serious in nature and only 1 of the patients experienced an interruption in therapy. The majority of the histamine- mediated adverse events were of mild (88.9%) or moderate (11.1%) intensity. *Nature of Risk*: There is the same fundamental concern of histamine-mediated events in pediatric patients as described in adult patients. Notably, none of the patients developed a respiratory event, including anaphylaxis, hypersensitivity, bronchospasm, or wheezing. All of the reported clinical events resolved by the end of the study.

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

Background Incidence / Prevalence	Infusion-related reactions associated with polyenes may not necessarily be histamine-related, but these infusion-related events are routinely associated with findings similar to those seen with histamine-related events. These events are: Infusion-related fever: • 17% with AmBisome™ • 44% with amphotericin B Infusion-related chills/rigors: • 18% with AmBisome™ • 54% with amphotericin B Infusion-related vomiting: • 6% with AmBisome™ • 8% with amphotericin B Infusion-related event: • 48.8% with AmBisome™ • 20.2% with amphotericin B Severe or moderately severe infusion-related event: • 32.0% with AmBisome™ 0.9% with amphotericin B [Ref. 5.4: 03QG04, 03PH5K] In the general population, the incidence of SJS/TEN is very rare. In a study of data from the UK-based Clinical Practice Research Datalink, there were 551 validated SJS/TEN patients, corresponding to an incidence rate of 5.76 SJS/TEN cases per million person-years between 1995 and 2013 [Ref. 5.4: 04T94R]. In a national medical insurance review system (Health Insurance Review and Assessment) database which contained the claims data for all of Korea from 2009 to 2013, the estimates of SJS and TEN were 3.96 to 5.03 in SJS and 0.94 to 1.45 in TEN per million [Ref. 5.4: 04T94V].
Risk Groups or Risk Factors	The risk factors for the development of these histamine-mediated events in either adult or pediatric patients are not entirely known. Patients who have demonstrated similar hypersensitivity-related events to prior exposure of caspofungin or other echinocandin agents (i.e., micafungin, anidulafungin) would remain at risk for developing similar reactions following the administration of caspofungin. Other theoretical risk factors would include patients who have known IgE-mediated allergy or histamine-mediated allergy to other drugs (i.e., Type I immediate hypersensitivity), patients with conditions that are associated with IgE overproduction (i.e., hyper IgE syndrome), or patients with disorders associated with mast cell overproduction (i.e., mastocytosis). The most common drug causes of SJS/TEN include sulfa drugs (cotrimoxazole, sulfasalazine), other antibiotics (aminopenicillins [usually ampicillin or amoxicillin], fluoroquinolones, cephalosporins), antiepileptics (phenytoin, carbamazepine, phenobarbital, valproate, lamotrigine) and other miscellaneous drugs (piroxicam, allopurinol, chlormezanone) [Ref. 5.4: 04T94S]. In a large epidemiology study, black and Asian patients were at a 2-fold risk of SJS/TEN when compared with white patients. Among patients with epilepsy and gout, odds ratios for SJS/TEN were significantly increased only in the presence of recent new drug treatment with antiepileptics or allopurinol, respectively [Ref. 5.4: 04T94R].

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

Potential Mechanisms	Caspofungin is a lipopeptide that fits into the category of basic polypeptides that can effectively cause histamine release from mast cells. In nonclinical safety assessment studies in rats and monkeys, rapid intravenous infusion was shown to cause physical signs related to histamine release. Preadministration of anti-histamine agents (e.g., cyproheptadine) eliminated or significantly curtailed the development of these events, thereby helping to confirm the histamine-mediated mechanism of action. Importantly, the prolongation of the infusion time also improved these findings. SJS/TEN are type IV hypersensitivity reactions which are a type of cell-mediated response. This delayed type of hypersensitivity reaction occurs when helper T cells are activated by antigen. If the antigen is presented a second time, the memory cells will lead to an inflammatory response which can result in tissue damage. The immune reaction can be triggered by medications and infections.		
Preventability	To avoid these events, caspofungin should never be administered by bolus infusion. Caspofungin should only be administered by a slow infusion over an approximately 1-hour time frame. In the event of a known hypersensitivity reaction, including histamine- mediated/anaphylactoid reaction following caspofungin, consideration could be given to using another antifungal agent. If the risk/benefit ratio for such a patient is in favor of continuing caspofungin therapy, consideration could be given to premedication with either diphenhydramine or other histamine blockers prior to subsequent doses of caspofungin may be considered for histamine-mediated hypersensitivity reactions. SJS/TEN are very rare events often associated with medications or infections, and primary prevention can be difficult since it is challenging to predict who will experience SJS/TEN. There can be a genetic predisposition to these events, and patients with a potential predisposition should inform their medical professional before initiation of any medications. For patients who experience SJS/TEN, it is generally recommended to avoid rechallenge with a medication associated with the SJS/TEN event.		
Impact on the Individual Patient	The impact of hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN on the individual patient depends upon the severity of the reaction. More common and less severe reactions such as skin reactions may cause discomfort but are not life threatening and will resolve. More severe reactions such as SJS/TEN can be life-threatening and require urgent attention.		
Potential Public Health Impact of Safety Concern	Considering that serious histamine-release events were infrequent and manageable in clinical trials, these events may not have public health implications.		
Evidence Source	***Adult Phase II/III Studies***	***Pediatric Studies***	***Post-marketing data***

Table 28 Details of Important Identified Risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

MedDRA Terms	*Clinical Terms* 1. Anaphylaxis 2. Hypersensitivity 3. Bronchospasm 4. Wheezing 5. Facial oedema 6. Pruritus or pruritus 7. Swelling face 8. Urticaria, 9. Flushing 10. Erythema 11. Rash, erythematous 12. Rash, pruritic generalized 13. Eosinophil count increased *Postmarketing Terms* 1. Anaphylaxis reaction 2. Hypersensitivity 3. Bronchospasm 4. Wheezing 5. Facial oedema 6. Pruritus or pruritus 7. Local Swelling 8. Urticaria, 9. Flushing 10. Erythema 11. Rash, erythematous 12. Rash, pruritic 13. Eosinophil count increased 14. Stevens-Johnson syndrome 15. Toxic epidermal necrolysis

Table 29 Details of Important Identified Risk: Drug resistance

Frequency with 95%CI	***Adult Phase II/III Studies*** In all the prior adult clinical trials, a total of 5 confirmed isolates of Candida spp. from 4 patients had reduced susceptibility to caspofungin. This included 3 C. albicans and 1 C. krusei isolates from 3 patients enrolled in the caspofungin empirical therapy study (Protocol 026) and 1 patient with C. albicans from the compassionate-use study (Protocol 024/025). All had higher MIC (minimum inhibitory concentrations) values for caspofungin and all had defined mutations in the FKS1 gene sequence following treatment with caspofungin. No Aspergillus isolates from clinical trials to date have shown evidence of reduced susceptibility, based on FKS1 testing. Through its surveillance program, the Applicant has also evaluated all isolates referred to Merck from marketed CANCIDAS® use since the first country approval in Dec- 2000 through 13-Feb-2006. A total of 12 confirmed isolates of Candida spp. from 9 patients with suspected reduced susceptibility to caspofungin have been identified. All had higher MIC values for caspofungin and defined mutations in the FKS1 gene sequence following treatment with caspofungin. No Aspergillus isolates referred from marketed CANCIDAS® use characterized to date have shown evidence of reduced susceptibility, based on FKS1 testing.	***Pediatric Studies*** To date, no Candida or Aspergillus isolates with confirmed caspofungin resistance have been reported in pediatric patients enrolled in the clinical trials.

Table 29 Details of Important Identified Risk: Drug resistance

Seriousness / Outcomes	***Adult Phase II/III Studies*** Drug resistance is likely to be associated with therapeutic failure, but is not directly associated with adverse clinical sequelae. **Postmarketing Data** In postmarketing review, 59 cases (60 events) were received for the adult population or with no reported age of the patient with the PT of the Drug resistance, 11 cases had confirmed laboratory data with no specific pattern of isolate resistance. . Of 59 cases, 54 were spontaneously reported and 5 were received through the non-interventional studies. Eighteen (18) cases were reported as serious and 42 as not serious. Eight (8) cases were received from the United States, 39 from EU and 12 from the rest of the world. The median age was 48 years old with the minimum of 20 years old and the maximum of 85years old. Thirteen (13) cases reported fatal outcome. Thirteen (13) cases reported outcome as not recovered, 7 as recovered/recovering and the rest of the cases reported the outcome as unknown.	***Pediatric Studies*** As described in adults **Postmarketing Data** In postmarketing review, 8 cases (8 events) were received for the pediatric population with the preferred term of the Drug resistance, 1 case had confirmed laboratory data. All cases were spontaneously reported, 4 were serious and 4 not serious. Two (2) cases were received from the United States, 3 from EU and 3 from the rest of the world. The median age was 14 years old with the minimum of 10 months old and the maximum of 17years old. Four (4) cases reported fatal outcome and 4 cases reported the outcome as unknown.
Severity and Nature of the Risk	***Adult Phase II/III Studies*** *Severity:* Severity grades do not apply to drug resistance. *Nature of Risk:* The occurrence of fungal resistance has been observed with most antimicrobial agents. It is considered an important event because it can result in propagation of the infection even in the setting of the antifungal agent. In this situation, a change in the antifungal regimen is routinely warranted to exact a treatment response.	***Pediatric Studies*** As described in adults

Table 29 Details of Important Identified Risk: Drug resistance

Background Incidence / Prevalence	Caspofungin MIC Values for Common *Candida* Species (µg/mL) MIC_{50} MIC_{90} Median MIC (range) *C. albicans* 0.01 – 1 0.12 – 1 0.5 (0.125 – >8) *C. glabrata* 0.06 – 0.5 0.25 – 1 1.0 (0.5 – 2) *C. parapsilosis* 0.125 – 2 1 – 4 2 (2 – >8) *C. tropicalis* 0.01 – 2 0.12 – 1 1.0 (0.5 – >8) *C. krusei* 0.5 – 2 0.5 – 2 2 (all values were 2) *C. lusitaniae* 0.5 – 2 *C. guilliermondii* 1 – >8 [Ref. 5.4: 03QG3P, 03QG3N, 03QG04] Caspofungin MIC Values for Common *Aspergillus* Species MIC range (ug/mL) *A. flavus* 0.03 – >8 *A. fumigatus* 0.03 – >8 *A. niger* 0.12 – 2 [Ref. 5.4: 03QG3N]		
Risk Groups or Risk Factors	There are no known intrinsic patient risk factors which would predispose certain patients to the development of caspofungin resistance. However, suboptimal daily doses of caspofungin (i.e., maintenance doses <50 mg daily in adults or <50 mg/m^2 daily in pediatric patients) or intermittent use of caspofungin (i.e., every other day or even less frequent dosing regimens) are anticipated to be risk factors for the development of resistance to caspofungin.		
Potential Mechanisms	Genetic experiments at Merck and other laboratories suggest that the *FKS1 gene* product is a key component in β (1,3)-D-glucan synthesis. Studies of several *Candida* species (including *C. albicans, C. glabrata,* and *C. krusei*) demonstrate that echinocandin resistance occurs primarily by mutations in certain key regions (i.e., amino acid sequence 640-650 and 640-650 1360-1365) of the *FKS1* gene. Echinocandin resistance is a rare event in the laboratory, occurring at about a rate of approximately 1 in 10^8 when selected on agar plates with drug. In *S. cerevisiae,* mutations in other genes such as *GNS1* can confer low level (≤10 x) resistance. Alterations to a second gene needed for sporulation, *FKS2,* occur only in strains already deficient in *FKS1*.		
Preventability	The only active measures to prevent the development of resistance with caspofungin would be to administer caspofungin at the recommended dose interval and duration described in the current EU SmPC. Less frequent daily maintenance dosages (i.e., <50 mg) and less frequent dosing intervals (i.e., every other day) should be avoided.		
Impact on the Individual Patient	If there is drug resistance then the drug will not be able to assist in resolving the fungal infection.		
Potential Public Health Impact of Safety Concern	Fungal resistance may be a cause for public health concern. Development of resistance can be associated with treatment failure in the individual, but also with transmission of a resistant fungal strain to other susceptible individuals. Administration of caspofungin should be as described in the current EU SmPC.		
Evidence Source	***Adult Phase II/III Studies***	***Pediatric Studies***	***Post-marketing data***
MedDRA Terms	*Clinical and PostmarketingTerm:* Drug resistance		

Table 30 Details of Important Identified Risk: Drug-drug interaction – Rifampin and other inducers of drug clearance

Frequency with 95%CI	***Adult Phase II/III Studies*** Not applicable. Patients on rifampin (or similar medication) and caspofungin are assumed to be subject to this DDI and thus are all recommended to have the dose of caspofungin adjusted.	***Pediatric Studies*** Not applicable. Pediatric patients on rifampin (or similar medication) and caspofungin are assumed to be subject to this DDI and thus are all recommended to have the dose of caspofungin adjusted.
Seriousness / Outcomes	***DDI studies*** The interaction between rifampin and caspofungin was examined in two separate studies in healthy subjects. In Protocol 032, in which the two compounds were administered concurrently, caspofungin levels increased initially but fell relative to single administration. A reduction in caspofungin trough levels was also noted in Protocol 035, in which subjects were pretreated 14 days with rifampin. Reduction in caspofungin concentrations is consistent with induction of biotransformation. An increase in the daily dose to 70 mg is expected to result in caspofungin concentrations that are comparable to those in the setting of caspofungin administered alone. ***Adult Phase II/III Studies*** Rifampin use was prohibited in the pivotal adult studies. **Postmarketing Data** In postmarketing review, events reported cumulatively through 01Jun2017 were retrieved from the global safety database utilizing the custom query of Drug interaction specific to Rifampin and other inducers of drug clearance. One case (1 event) was received for the adult population during this time period with the PT of the Drug interaction and concomitant use of rifampin. The case was a non-serious, spontaneously reported case from the United States. The case reported potential drug interaction resulting in treatment failure but contained limited information. The case was confounded by patient's underlying disease.	***Pediatric Studies*** Rifampin use was prohibited in the pivotal pediatric studies. **Postmarketing Data** In postmarketing review, events reported cumulatively through 01Jun2017 were retrieved from the global safety database utilizing the custom query of Drug Interaction specific to Rifampin and other inducers of drug clearance. One case (1 event) was received for the pediatric population during this time period, with the PT of the Drug interaction and concomitant use of rifampin. The case was a serious spontaneously reported case from France regarding a PPD patient. This case reported potential drug interaction with rifampin and the patient experienced potential nephrotoxicity; The case was confounded by patient's underlying disease as well as multiple concomitant medications. The outcome was reported as recovered.

Table 29 Details of Important Identified Risk: Drug resistance

Severity and Nature of the Risk	A dedicated drug-drug interaction study in healthy subjects demonstrated a 30% decrease in caspofungin trough concentrations. Patients on concomitant rifampin therapy should consider increasing their dose of caspofungin to 70 mg daily of. When caspofungin is co-administered with other inducers (efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine), a daily dose of 70 mg caspfungin should be considered.	Pediatric patients on rifampin should receive 70 mg/m^2 daily of caspofungin (maximum dose 70 mg). When caspofungin is co-adminstered with other inducers of drug clearance (efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine), a daily dose of 70 mg/m^2 caspfungin should be considered.
Background Incidence / Prevalence	Not available.	
Risk Groups or Risk Factors	All patients taking caspofungin and rifampin (or similar medication) are subject to this DDI.	
Potential Mechanisms	Rifampin is a strong inducer of hepatic enzymes and an inhibitor of transport via OATP1B (single-dose). As the in vitro data do not demonstrate metabolism of caspofungin by CYP enzymes but do show low affinity transport of caspfungin via OATP1B1, this DDI is likely due to effects on OATP1B1.	
Preventability	The DDI cannot be prevented. Increasing the dose of caspofungin may compensate for the effects of the DDI.	
Impact on the Individual Patient	Patients on rifampin or similar drugs should consider increasing their dose of caspofungin when on concomitant therapy with rifampin and other inducers of drug clearance.	
Potential Public Health Impact of Safety Concern	Considering that this DDI is infrequent and manageable as seen in postmarketing experience, the DDI may not have public health implications.	
Evidence Source	***DDI studies and post-marketing data***	
MedDRA Terms	*Postmarketing Terms* Drug interaction	

Table 31 Details of Important Identified Risk: Drug-drug interaction - Cyclosporin A

Frequency with 95%CI	***Adult Phase II/III Studies*** Not applicable. Patients on cyclosporin A and caspofungin are assumed to be subject to this DDI.	***Pediatric Studies*** Not applicable. Pediatric patients on cyclosporin A and caspofungin are assumed to be subject to this DDI.
Seriousness / Outcomes	***DDI Studies*** Two dedicated DDI trials (P013, P017) were performed that examined the two-way interaction between caspofungin and cyclosporin A(CsA). In P013, caspofungin was administered with a single 4 mg/kg dose of cyclosporin A, while in P017 caspofungin was administered with two 3 mg/kg doses 12 hours apart, In both studies, caspofungin exposure levels were ~30% higher when administered with cyclosporin A. ***Adult Phase II/III Studies*** Cyclosporin A use was prohibited in the pivotal adult studies. Four patients in the salvage Aspergillus study (Protocol 019) and 2 patients in the compassionate use study (Protocol 024/025) have received caspofungin and cyclosporin A for 2 to 56 days. There were no elevations in liver enzymes observed during daily monitoring. **Postmarketing Data** In postmarketing review, events reported cumulatively through 01Jun2017 were retrieved from the global safety database utilizing the custom query of Drug interaction specific to Cyclosporin A. During that period, 10 cases (21 events) were received for the adult population or with no reported age of the patient that matched the query. Most common PT' reported (N ≥ 2) were Drug interaction (N=5) and Drug level increased (N=3) All cases were spontaneously reported. Five (5) cases were reported as serious and 5 as non-serious. Three (3) cases were received from the United States, 3 from EU and 4 from the rest of the world. The median age was 61 years of age with the minimum of 34 years and the maximum of 68 years]. Two (2) cases reported fatal outcome. Both cases reported patients with severe underlying conditions and comorbidities that led to fatal outcome.	***Pediatric Studies*** Cyclosporin A use was prohibited in the pivotal pediatric studies. **Postmarketing Data** In postmarketing review, events reported cumulatively through 01Jun2017 were retrieved from the global safety database utilizing the custom query of Drug interaction specific to Cyclosporin A. During that period, 1 case (7 events) was received for the pediatric population that matched this query. The case was serious and spontaneously reported from Italy regarding a PPD . The time to onset (TTO) was not reported. The outcome was reported as fatal. The case was confounded by the patient's severe underlying conditions and comorbidities that led to fatal outcome.

Table 31 Details of Important Identified Risk: Drug-drug interaction - Cyclosporin A

	The time to onset (TTO) was reported in 4 cases (8 events). The median TTO was reported as 17 days with the minimum of 2 days and the maximum of 55 days. Five (5) cases reported outcome as recovered/recovering and one case reported the outcome as unknown.	
Severity and Nature of the Risk	In two adult clinical studies, cyclosporin A (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by 34%. Caspofungin did not increase the plasma levels of cyclosporin A. There were transient increases in liver ALT and AST when caspofungin and cyclosporin A were co-administered.	The effect of cyclosporin A on caspofungin in pediatric patients has not been examined, but it is likely that pediatric patients would demonstrate a similar effect.
Background Incidence / Prevalence	Incidence of patients taking CsA and caspofungin concomitantly is unavailable. However, evidence from observational studies suggests that concomitant use of caspofungin and CsA in the clinical setting, where CsA levels are monitored, is generally well tolerated and benefits outweigh the risks [Ref. 5.4: 03PS4H, 04TMT7, 04TMSW, 03PPGF, 04TV6V]. A retrospective chart review study of 40 immunocompromised, medically complicated patients in the US who received caspofungin and CsA concomitantly reported no serious adverse events occurred because of caspofungin. There were 4 patients who discontinued therapy, 2 of whom discontinued because of hepatotoxicity possibly related to concomitant use of caspofungin and CsA [Ref. 5.4: 03PS4H]. In a Japanese study of 28 allogeneic hematopoietic stem cell transplant (HSCT) patients, concomitant administration of caspofungin and CsA revealed that caspofungin increased CsA concentration yet there was no significant clinical impact (detailed drug interaction analyses could be performed in 16 of the patients who received CsA) [Ref. 5.4: 04TMSW]. A separate study that included 7 liver transplant patients treated concomitantly with a 14 day course of caspofungin and CsA reported no liver enzyme elevation and no hepatotoxicity [Ref. 5.4: 04TMT7]. A Spanish study of 14 patients reported that co-administration of caspofungin and CsA was generally well tolerated [Ref. 5.4: 03PPGF]. A study of 3 lung transplant patients receiving CsA reported that co-administration with caspofungin was well tolerated [Ref. 5.4: 04TV6V].	
Risk Groups or Risk Factors	All patients taking caspofungin and cyclosporin A are subject to this DDI.	
Potential Mechanisms	Cyclosporin A likely increases caspofungin concentrations through inhibition of the transporter- mediated (OATP1B1) uptake of caspofungin into hepatocytes.	
Preventability	The OATP1B1 effect mediated by cyclosporin A is not preventable.	
Impact on the Individual Patient	Because high levels of caspofungin are associated with elevated liver enzymes (see Table 27), patients on cyclosporin A and caspofungin may be at higher risk for elevated liver enzymes. Monitor patients who develop abnormal liver enzymes during concomitant therapy and evaluate the risk/benefit of continuing therapy.	
Potential Public Health Impact of Safety Concern	Considering that this DDI is infrequent and manageable as seen in postmarketing experience, the DDI may not have public health implications.	
Evidence Source	***DDI studies and post-marketing data***	
MedDRA Terms	*Postmarketing Terms* Drug interaction	

Table 32 Details of Important Identified Risk: Drug-drug interaction – Tacrolimus

Frequency with 95%CI	***Adult Phase II/III Studies*** Not applicable. Patients on tacrolimus and caspofungin are assumed to be subject to this DDI.	***Pediatric Studies*** Not applicable. Pediatric patients on tacrolimus and caspofungin are assumed to be subject to this DDI.
Seriousness / Outcomes	***DDI Studies*** In P017, the two-way interaction between caspofungin and tacrolimus was examined. There was no change in the PK of caspofungin with co-administration, but levels of tacrolimus were ~20% lower in subjects also administered caspofungin. Given the narrow therapeutic index of tacrolimus, this small difference is potentially clinically significant. ***Adult Phase II/III Studies*** In the CANCIDAS salvage Aspergillus study eighteen patients received tacrolimus and caspofungin concomitantly, of whom 8 also received mycophenolate mofetil. Reports of decreased tacrolimus levels were observed. However, increased tacrolimus levels are difficult to interpret in acutely ill patients receiving a number of concomitant medications. **Postmarketing Data** In postmarketing review, events reported cumulatively through 01Jun2017 were retrieved from the global safety database utilizing the custom query of Drug Interaction specific to Tacrolimus. During that period, 8 cases (26 events) were received for the adult population or with no reported age of the patient that matched the query. Most common PT' reported (N ≥ 2) were Drug interaction (N=4); Drug level increased (N=3); Drug level decreased (N=2) and Leukopenia (N=2) One (1) case was reported from non-interventional studies and 7 cases were spontaneously reported. Five (5) cases were reported as non-serious and 3 as serious. One (1) case was received from the United States, 3 from EU and 4 from the rest of the world. The median age was 52 years of age with the minimum of 23 years of age and the maximum of 65 years of age.	***Pediatric Studies*** In two pediatric studies, in subjects 3 months <17 years of age, one investigating caspofungin as empirical therapy in pediatric subjects with persistent fever/ neutropenia (2 <17 years), and one investigating documented candida and aspergillus infections (3 months<17 years). Five subjects in total had concomitant tacrolimus use with caspofungin. No tacrolimus levels decreased or toxicities were reported. **Postmarketing Data** In postmarketing review, events reported cumulatively through 01Jun2017 were retrieved from the global safety database utilizing the custom query of Drug interaction specific to Tacrolimus. During this period, 4 cases (17 events) were received for the pediatric population that matched the query. Most common PT reported (N ≥ 2) was Drug Interaction. One (1) case was reported from non-interventional studies and 3 cases were spontaneously reported. Three (3) cases were reported as serious and 1 case was reported as non-serious. One (1) case was received from the United States, 2 from EU and 1 from the rest of the world. The median age was 8 years of age with the minimum of 5 years of age and the maximum age of 14 years of age. One (1) case reported fatal outcome. The case was confounded by patient's preexisting conditions, severe comorbidities and concomitant medications. One (1) case reported outcome as recovered, 1 case reported outcome not recovered and 2 cases reported outcome as unknown. The time to onset (TTO) was reported in 1 case (4 events). The drug interaction TTO was reported as 9 days.

Table 32 Details of Important Identified Risk: Drug-drug interaction – Tacrolimus

	The time to onset (TTO) was reported in 3 cases (12 events). The median TTO was reported as 146 days with the minimum of 4 days and the maximum of 160 days. One (1) case reported a fatal outcome. The case was confounded by patient's preexisting conditions and multiple concomitant medications. Three (3) cases reported outcome as recovered/recovering and the remaining 4 cases reported the outcome as unknown.	
Severity and Nature of the Risk	Tacrolimus levels should continue to be monitored, in accordance with standard recommendations, while patients are on both caspofungin and tacrolimus. Following these levels will allow clinicians to determine whether patients receiving concurrent caspofungin therapy require tacrolimus dose adjustments.	Tacrolimus levels should continue to be monitored, in accordance with standard recommendations, while patients are on both caspofungin and tacrolimus. Following these levels will allow clinicians to determine whether patients receiving concurrent caspofungin therapy require tacrolimus dose adjustments.
Background Incidence / Prevalence	Incidence of patients taking tacrolimus (TAC) and caspofungin concomitantly is unavailable. Evidence from observational studies suggests that co- administration of caspofungin and TAC, in the clinical setting where TAC levels are presumably well monitored, is generally well tolerated and the benefits outweigh the risks [Ref. 5.4: 04TMSW, 04TV6V, 04TMT7]. A Japanese study of 34 allogeneic HSCT patients who were treated with caspofungin and TAC concomitantly revealed that there was no change in plasma concentration/dose ratio of TAC before and after the co-administration of drugs [Ref. 5.4: 04TMSW]. The authors report that drug interactions between TAC and caspofungin did not appear to be a problem. A small study of 9 lung transplant patients receiving TAC reported that co-administration with caspofungin was well tolerated [Ref. 5.4: 04TV6V]. A study that included 5 liver transplant patients treated concomitantly with caspofungin and TAC reported no liver enzyme elevation and no hepatotoxicity in the 3 patients who received a 14-day course of capsofungin therapy (2 patients died prior to completing capsofungin therapy and the deaths were not considered to be related to the co-therapy of caspofungin and TAC) [Ref. 5.4: 04TMT7].	
Risk Groups or Risk Factors	All patients on caspofungin and tacrolimus are subject to this DDI.	
Potential Mechanisms	The mechanism is unclear. However, tacrolimus is metabolized extensively in human via CYP pathways, including CYP3A4. Extensive distribution into tissues and into blood cells also has a substantial role in tacrolimus disposition. Although the reduced tacrolimus levels are consistent with an induction mechanism, caspofungin does not induce CYP3A4. Displacement of tacrolimus binding in blood by caspofungin may be the mechanism of the observed interaction. As the distribution of tacrolimus into red blood cells is nonlinear, a very modest displacement of tacrolimus binding into blood by caspofungin could result in the reduced whole-blood concentrations observed.	
Preventability	The DDI between caspofungin and tacrolimus is not preventable.	
Impact on the Individual Patient	As this DDI potentially results in decreased levels of tacrolimus, patients on caspofungin and tacrolimus should continue to be monitored. A lack of monitoring and/or not changing tacrolimus dosing appropriately in response to decreased levels may result in decreased efficacy of tacrolimus as an immunosuppressant.	

Table 32 Details of Important Identified Risk: Drug-drug interaction – Tacrolimus

Potential Public Health Impact of Safety Concern	Considering that this DDI is infrequent and manageable as seen in postmarketing experience, the DDI may not have public health implications.
Evidence Source	***DDI studies and post-marketing data***
MedDRA Terms	*Postmarketing Terms* Drug interaction

SVII.4 Identified and Potential Interactions

Overview of Potential for Interactions

Based on both in vivo and in vitro studies, caspofungin does not appear to be a P-glycoprotein (P-gp) substrate. In additional in vitro studies, Cyclosporin A, a potent and specific P-gp inhibitor, did not affect the accumulation of labeled caspofungin, further supporting that caspofungin is not a substrate for P-gp. Caspofungin also does not act as a P-gp inhibitor, based on in vitro assessments.

The role of transporters in the hepatic uptake of caspofungin was assessed utilizing heterologously expressed liver transporters. Significant caspofungin uptake (up to 60 min) was observed in cells overexpressing OATP-C, but not in cells overexpressing OATP-8 (OATP1B3). These findings suggest that caspofungin is a low-affinity substrate for OATP-C (OATP1B1) and that this hepatic uptake is a slow process. The inhibitory effect of caspofungin on hepatic transporters OATP1B1, NTCP, OCT1 and OAT1 was evaluated at 10 and 100 μM. Caspofungin did not inhibit the transporters at 10 μM (a clinically relevant concentration), but at 100 μM (in excess of clinical concentrations) there appeared to be slight inhibition of these uptake transporters.

Metabolic pathways were assessed in preclinical studies of mouse, rat, rabbit and monkey. Plasma extracts during the initial 24 hours consisted predominantly of the unchanged drug and a small amount of a hydrolytic product, L-000747969, which was the major circulating product at later time-points (Days >3). Urine samples from mice, rats, rabbits, monkeys, and humans revealed that the urine contained mainly the polar hydrolytic metabolites, M1 (4(S)-hydroxy-4-(4-hydroxyphenyl)-L-threonine) and M2 (*N*-acetyl-4(S)-hydroxy-4-(4-hydroxyphenyl)-L-threonine). Collectively, these results indicated that the main metabolic pathway of caspofungin involved peptide hydrolysis and *N*-acetylation in all species studied. Qualitatively and quantitatively, the metabolic pathway and metabolites of caspofungin in the animal species were similar to the findings in humans.

To identify the enzyme systems (CYP and hydrolytic enzymes, such as amidase, peptidase, and proteases) potentially involved in the metabolism of caspofungin, additional in vitro studies were performed, and the results indicated that caspofungin is a poor substrate for both the major CYP isozymes and the hydrolytic enzymes tested. Neither caspofungin nor its major metabolite (L-000747969) is a potent inhibitor of the CYP isozymes tested (CYP1A2,

2A6, 2C9, 2C19, 2D6, and 3A4). In addition, no drug-drug interactions were observed in rats when caspofungin was administered concurrently with either indinavir (a compound extensively metabolized by CYP3A1/2), or ketoconazole (a potent CYP3A inhibitor). Two additional studies were performed to evaluate potential drug-drug interaction (DDI) between caspofungin and either amphotericin B (AmB) or cyclosporin A (CsA). In a 14-day caspofungin and AmB interaction study, coadministration of AmB had no effect on the steady-state kinetics of caspofungin; conversely, coadministration of caspofungin did not affect the steady-state kinetics of AmB. Coadministration of CsA appeared to have a slight but significant effect on the pharmacokinetics of caspofungin, as the Day 14 trough plasma concentrations and AUC0-24 hr values were 27 and 16% higher, respectively, in the group that received CsA, likely secondary to reduced hepatic uptake of caspofungin.

Seven dedicated caspofungin DDI trials were performed in healthy human subjects. These trials demonstrated no clear effect on caspofungin AUC after co-administration of itraconazole, AmB, tacrolimus, mycophenolate, nelfinavir, or rifampin. As noted below, treatment with CsA resulted in an increase in AUC, while treatment with rifampin led to a decrease in C24hr. Also noted below, there was a modest decrease in tacrolimus levels after co-administration of caspofungin; caspofungin had no effect on levels of the other compounds listed above.

Important Identified and Potential Interactions

Table 33 Identified / Potential Interaction(s) with Other Medicinal Products, Food and Other Substances

Interacting substance	Rifampin and other inducers of drug clearance (e.g. nevirapine, phenytoin, dexamethasone, carbamazepine, efavirenz)
Effect of interaction	Drug levels decreased (of caspofungin)
Evidence source	Rifampin co-administered with caspofungin modestly lowered caspofungin plasma concentrations by approximately 30%. Rifampin pharmacokinetics were unaltered. Regression analysis of patients pharmacokinetic data suggest co-administration of other drug clearance inducers (e.g. nevirapine, phenytoin, dexamethasone, carbamazepine, efavirenz) with caspofungin may result in reduction in caspofungin concentrations.
Possible mechanisms	Rifampin appears to reduce caspofungin concentration via induction of the transporter-mediated (OATP1B1) uptake of caspofungin into cells, including hepatocytes. Of note, clinical studies indicate that rifampin is both an inducer and inhibitor of this uptake transport, with a slight net inductive effect, as stated above, at steady-state. For other inducers, mechanisms are unknown.
Potential health risk	Co-administration of caspofungin with drugs that induce drug clearance, such as rifampin or other inducers, reduces caspofungin plasma concentrations and could decrease its therapeutic effect.
Discussion	Clinical data with caspofungin indicate that reductions in plasma concentrations on the order of that seen with rifampin could be associated with decreased efficacy. A dose increase of caspofungin to 70 mg daily should be considered when co-administered with inducer drugs that lower plasma concentrations of caspofungin. These observations are reflected in the product circular.

Table 34 Identified / Potential Interaction(s) with Other Medicinal Products, Food and Other Substances

Interacting substance	Cyclosporin A
Effect of interaction	Drug levels increased (of caspofungin)
Evidence source	Cyclosporine A co-administered with caspofungin modestly increases caspofungin plasma concentrations by approximately 34%. Cyclosporine A pharmacokinetics were unaltered.
Possible mechanisms	Cyclosporine A appears to increase caspofungin concentrations through inhibition of the transporter- mediated (OATP1B1) uptake of caspofungin into cells, including hepatocytes. A rat model of this drug interaction demonstrated reduced caspofungin concentrations in liver in the presence of coadministered cyclosporine A.
Potential health risk	Co-administration of caspofungin with drugs that inhibit OATP1B1 such as cyclosporine, increase plasma concentrations of caspofungin.
Discussion	A dose adjustment of caspofungin is not required when co- administered with drugs that modestly increase plasma concentrations of caspofungin such as Cyclosporine A. These observations are reflected in the product circular.

Table 35 Identified / Potential Interaction(s) with Other Medicinal Products, Food and Other Substances

Interacting substance	Tacrolimus
Effect of interaction	Drug levels decreased (of tacrolimus)
Evidence source	Tacrolimus co-administered with caspofungin had no effects on plasma concentrations of caspofungin. Plasma concentrations of tacrolimus were, however, decreased by approximately 20%.
Possible mechanisms	The mechanism for the interaction with tacrolimus is unknown.
Potential health risk	Immunosuppressive effects of tacrolimus maybe reduced with decreased concentrations of tacrolimus.
Discussion	No dose adjustment for caspofungin is required. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended. These observations are reflected in the product circular.

SVII.5 Pharmacological Class Effects

Caspofungin is a member of the echinocandin antifungal class. Echinocandins are potent inhibitors of β-(1,3)-D-glucan synthesis, which is essential for cell wall integrity of many pathogenic fungi such as *Candida* and *Aspergillus*. The inhibition of β-(1,3)-D-glucan synthesis results in osmotic fragility of susceptible fungi and causes cell lysis. Based on their unique mechanism of action, caspofungin and other members of the echinocandin class remain active against *Candida* isolates resistant to other antifungal agents.

SVII.5.1 Pharmacological Class Risks Already Included as Important Identified or Potential Risks

There are currently 2 other echinocandins approved in the EU: anidulafungin (ECALTA™, Pfizer) and micafungin (MYCAMINE™, Astellas Pharmaceuticals). Due to the differing risks associated with each product, each is described separately.

Anidulafungin (ECALTA™)
Anidulafungin is approved for the use in the treatment of adult patients with invasive candidiasis. Anidulafungin was approved by the EMEA in Sep-2007. Therefore, the information on anidulafungin is limited to the available data in the ECALTA™ Product Circular or the Scientific Discussion released by the EMEA following the ECALTA™ approval. As with caspofungin, hepatic events (as manifested by transaminase elevations) and histamine-mediated (or infusion-related) adverse events have been seen with anidulafungin. There have not been controlled clinical trials directly comparing caspofungin and anidulafungin. The information below is drawn from respective product information.

- Asymptomatic, reversible elevations in transaminases were seen in both the caspofungin and anidulafungin Phase II/III trials in patients. It is difficult to compare the ALT/AST data directly as the data were collected from patients with different underlying medical conditions and receiving echinocandin for different treatment indications; however, the incidence of ALT or AST elevations was <10% with both products.
- Infusion-related events occurred in a similar proportion of patients receiving caspofungin or anidulafungin: anaphylaxis 0.1% vs. <1%, hypersensitivity 0.1%, vs. <1%, bronchospasm 0.1% vs. <1%, flushing 1.4% vs. 1.5%, pruritus 1.2% vs. 1.0%, wheezing 0.2% vs. <1%, erythema 0.7% vs. <1%, facial edema 0.1% vs. <1%, and urticaria 0.4% vs. <1%, respectively.

Three other important potential risks identified in the EMEA Scientific Discussion for anidulafungin include convulsions, QT prolongation, and anesthetic exacerbation of infusion-related adverse events. Anesthetic exacerbation of infusion-related adverse events was confirmed only in preclinical studies. None of these events have been seen in caspofungin clinical trials to date, as noted below. Anidulafungin is not approved for use in pediatric patients. As there are no available safety data on the use of anidulafungin in pediatric patients, pharmacological effects due to anidulafungin in the pediatric patient population have not been identified. Notably, none of the other important potential risks noted for anidulafungin (convulsions, anesthetic exacerbation of infusion-related adverse events, and QT prolongation) were reported in any of the 171 pediatric patients included in the caspofungin pediatric studies.

There is no data in the ECALTA™ Product Circular regarding the use of anidulafungin at higher-than-approved doses. Notably, none of the other important potential risks noted for anidulafungin (convulsions, anesthetic exacerbation of infusion-related adverse events, and

QT prolongation) were reported in any of the 100 adult patients who received caspofungin at 150 mg daily (in Protocol 801).

In postmarketing experience (including compassionate use not associated with a clinical trial) as of 01-Jun-2017, a small number of reports of electrocardiogram QT prolongation and/or torsades de pointes and convulsions were identified for caspofungin. Majority of reports of QT prolongation/torsades with sufficient information for evaluation, the patients (all adults) were taking one or more concomitant medications which have been associated with QT prolongation (e.g. fluoroquinolone or macrolide antibiotics). In most reports of convulsions, alternative explanations for the adverse event were identified (e.g. concomitant carbapenem antibiotics, concurrent medical conditions associated with convulsions such as meningitis, cerebral hemorrhage, or brain lesions), majority of reports of convulsion were in adults.

Micafungin (MYCAMINE™)
Micafungin is approved for the use in the treatment of adult and pediatric patients with invasive candidiasis or as prophylaxis against *Candida* infections in patients undergoing allogeneic hematopoietic stem cell transplantation or patients who are expected to have neutropenia for 10 or more days. Micafungin is also approved for use in adult patients (≥16 years of age) with esophageal candidiasis in whom intravenous therapy is appropriate. Micafungin was approved by the EMEA in May-2008. Therefore, the information on micafungin is limited to the data in the MYCAMINE™ Product Circular or the Scientific Discussion released by the EMEA following the MYCAMINE™ approval. As with caspofungin, hepatic events (as manifested by transaminase elevations) and histamine-mediated (or infusion-related) adverse events have been seen with micafungin. Although comparative studies have been conducted with caspofungin and micafungin, safety data is not available from these studies. Therefore, the information below is drawn from respective product information.

- Asymptomatic, reversible elevations in transaminases were seen in both the caspofungin and micafungin Phase II/III trials. It is difficult to compare the ALT/AST data directly as the data were collected from patients with different underlying medical conditions and receiving echinocandin for different treatment indications; however, the incidence of ALT or AST elevations was <10% with both products.
- Histamine-mediated allergic events occurred in a similar proportion of patients receiving caspofungin or micafungin: anaphylaxis 0.1% vs. <1%, hypersensitivity 0.1%, vs. <1%, bronchospasm 0.1% vs. <1%, flushing 1.4% vs. <1%, pruritus 1.2% vs. 0.8%, wheezing 0.2% vs. <1%, erythema 0.7% vs. <1%, facial edema 0.1% vs. <1%, and urticaria 0.4% vs. <1%, respectively.

Other important potential risks identified in the EMEA Scientific Discussion for micafungin include hemolytic adverse experiences, pancytopenia, renal adverse experiences, liver tumors, effects on the male reproductive tract, reproductive and developmental toxicity, and development of resistant strains. Liver tumors, effects on the male reproductive tract, and reproductive and developmental toxicity were only confirmed in preclinical studies. Only the

event of drug resistance (development of resistant strains) has been seen in caspofungin clinical trials to date.

Micafungin is approved for use in pediatric patients (0 to 16 years of age). Pharmacological effects specifically pertaining to the pediatric patient population have not been identified for micafungin. The MYCAMINE™ Product Circular notes that some adverse reactions, such as vomiting, abdominal pain, pruritus, thrombocytopenia, hyperbilirubinemia, hepatomegaly, tachycardia, hypertension, hypotension and renal adverse reactions are more commonly seen in the pediatric population than in older patients. Specifically, increases in ALT, AST, and alkaline phosphatase following micafungin use occur in a higher proportion of patients <1 year of age. Similar elevations were not reported for pediatric patients receiving caspofungin. Additionally, none of the other important potential risks noted for micafungin (hemolytic adverse experiences, pancytopenia, and liver tumors) were reported in any of the 171 pediatric patients included in the caspofungin pediatric studies.

The MYCAMINE™ Product Circular reports the use of micafungin at higher-than-approved doses up to 8 mg/kg (maximum total dose of 896 mg). No adverse reactions associated with the higher doses of micafungin have been reported. Notably, none of the other important potential risks noted for micafungin (hemolytic adverse experiences, pancytopenia, and liver tumors) were reported in any of the 100 adult patients who received caspofungin at 150 mg daily (in Protocol 801).

In postmarketing experience (including compassionate use not associated with a clinical trial), as of 01-Jun-2017, a small number of reports of hemolytic adverse events and pancytopenia were identified for caspofungin. Most reports of hemolytic adverse event reports provided sufficient information for evaluation. Of these reports, one concerned a patient who was taking a concomitant medication (dapsone) which has been associated with hemolytic anemia, and others involved concurrent medical conditions associated with hemolysis (sepsis, leukemia) or included minimal information. Most of the hemolytic adverse events were in adults. In majority of reports of pancytopenia that provided sufficient information for analysis, alternative explanations for the adverse event were identified (e.g. concomitant medications such as flucytosine, meropenem, voriconazole and/or concurrent medical conditions such as sepsis), most were reports in adult population. Through 01-Jun-2017, multiple reports of drug resistance (important identified risk) have been received with use of caspofungin and are further discussed in Table 29.

SVII.5.2 Important Pharmacological Class Effects Not Discussed Above

Not applicable

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 3.2

Table 36 Summary of Safety Concerns

Important identified risks	▪ Increase in liver enzymes ▪ Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN ▪ Drug resistance ▪ Drug-drug interaction: Rifampin and other inducers of drug clearance ▪ Drug-drug interaction: Cyclosporin A ▪ Drug-drug interaction: Tacrolimus
Important potential risks	▪ None
Missing information	▪ Exposure during pregnancy ▪ Additional data on the safety and effectiveness in neonates and infants <3 months of age

PART III PHARMACOVIGILANCE PLAN

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 3.2

Routine Pharmacovigilance
The MAH maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports, PSURs, etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

III.1 Safety Concerns and Overview of Planned Pharmacovigilance Actions

Table 37 Overview of Pharmacovigilance Actions

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Important identified risk: Increase in liver enzymes		
Routine evaluation and monitoring of reports of increased liver enzymes and related hepatic events in adult and pediatric patients	Routine Pharmacovigilance	To monitor, identify, and evaluate reports of increased liver enzymes and related hepatic events, in adult and pediatric patients treated with caspofungin.
Important identified risk: Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN		
Evaluation and monitoring of reports of hypersensitivity reactions including histamine- mediated allergic reactions and SJS and TEN in adult	Routine Pharmacovigilance	To monitor, identify, and evaluate reports of hypersensitivity reactions including histamine-mediated allergic reactions, and SJS/TEN in patients treated with caspofungin.

Table 37 Overview of Pharmacovigilance Actions

Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
and pediatric patients		
Important identified risk: Drug resistance		
Evaluation and monitoring of reports of drug resistance to caspofungin in adults and pediatric patients	Routine Pharmacovigilance	To monitor, identify, and evaluate reports of drug resistance to caspofungin in adults and children treated with caspofungin.
Important identified risk: Drug-drug interaction: Rifampin and other inducers of drug clearance		
Evaluation and monitoring of reports of drug interaction with rifampin and other inducers of drug clearance	Routine Pharmacovigilance	To monitor, identify, and evaluate reports of drug interaction with rifampin and other inducers of drug clearance in adult and pediatric patients treated with caspofungin.
Important identified risk: Drug-drug interaction: Cyclosporin A		
Evaluation and monitoring of reports of drug interaction with cyclosporine A	Routine Pharmacovigilance	To monitor, identify, and evaluate reports of drug interaction with cyclosporine A in adult and pediatric patients treated with caspofungin.
Important identified risk: Drug-drug interaction: Tacrolimus		
Evaluation and monitoring of reports of drug interaction with tacrolimus	Routine Pharmacovigilance	To monitor, identify, and evaluate reports of drug interaction with tacrolimus in adult and pediatric patients treated with caspofungin.
Important Missing Information: Exposure during pregnancy		
Evaluation and monitoring of reports of exposure during pregnancy	Routine Pharmacovigilance	To collect information on exposure to caspofungin during pregnancy, to allow for identification of pregnancy outcomes and maternal/fetal/newborn adverse events.
Important Missing Information: Additional data on the safety and effectiveness in neonates and infants < 3 months of age		
Evaluation and monitoring of reports of exposure of neonates and infants < 3 months of age	Routine Pharmacovigilance	To collect additional data on the safety and effectiveness of caspofungin in the treatment of neonates and infants < 3 months of age

III.2 Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimization Measures

No additional risk minimization measures are proposed for caspofungin acetate.

III.3 Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

Caspofungin acetate is being monitored under routine pharmacovigilance.

No additional pharmacovigilance activities from this Pharmacovigilance Plan have been completed since the last version of this RMP.

III.4 Details of Outstanding Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities proposed for caspofungin acetate.

III.5 Summary of the Pharmacovigilance Plan

Caspofungin acetate is being monitored under routine pharmacovigilance.

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 2.0

There are no additional planned post-authorization efficacy studies for caspofungin.

IV.1 Applicability of Efficacy to All Patients in the Target Population

There are no adequate and well-controlled studies of caspofungin in pregnant or breast-feeding women. Patients who were pregnant or breast-feeding were excluded from clinical trials. In addition, patients with acute hepatitis, cirrhosis, or moderate or severe hepatic insufficiency due to any cause were excluded from all the clinical trials (adults and pediatric).

Although caspofungin has been examined in neonates and infants <3 months of age in a prospective pharmacokinetic study (Protocol 058), the safety and efficacy data for caspofungin in this age group remain limited.

IV.2 Tables of Post-authorization Efficacy Studies

The efficacy / effectiveness of caspofungin acetate in the indications for treatment of: invasive candidiasis, invasive aspergillosis in patients refractory to or intolerant of other therapy (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole), empirical treatment of presumed fungal infections (such as Candida and Aspergillus spp.) in febrile, neutropenic, and esophageal candidiasis] has been adequately evaluated in the completed clinical study program, and no additional post-authorization efficacy studies (PAES) are required to support the use of caspofungin as described in the approved SmPC.

IV.3 Summary of Post-authorization Efficacy Development Plan

There are no ongoing or proposed post-authorization efficacy studies (PAES) for caspofungin acetate.

IV.4 Summary of Completed Post-authorization Efficacy Studies

There are no completed post-authorization efficacy studies (PAES) for caspofungin acetate.

PART V RISK MINIMIZATION MEASURES

Active substance(s): Caspofungin acetate

Product(s) concerned: CANCIDAS®

MAH / MAA name: Merck Sharp & Dohme Ltd.

Data lock point for this module: 01-JUN-2017

RMP version number when this module was last updated: 3.2

V.1 Risk Minimization Measures by Safety Concern

Table 38 Risk Minimization Plan for Increase in liver enzymes

Safety Concern	Important identified risk
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that reports of increased liver enzymes and related hepatic events in adult and pediatric patients treated with caspofungin have been reported in clinical studies and in the postmarketing environment and a separate dosage regimen for some patients with hepatic impairment is provided. Additionally, cyclosporin A interaction is noted as a potential risk factor for increase in liver enzymes and appropriated language is included in the product labeling.
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.2: Posology and method of administration – Special populations – Hepatic impairment Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 4.8: Undesirable effects
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reported AEs are consistent with the known safety profile of CANCIDAS® as noted in the SmPC. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 39 Risk Minimization Plan for Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN

Safety Concern	Important identified risk
Objective(s) of the Risk Minimization Measure(s)	The objectives of this routine risk minimization measures are to: 1) inform healthcare providers and patient caregivers of the risk of hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN following administration of CANCIDAS®; 2) identify potential risk factors for hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN in the recipient's history; 3) provide appropriate advice to healthcare providers and patient caregivers in order to minimize the risk in clinical practice; 4) inform recipients and/or caregivers of recipients of the risk of hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN following administration of CANCIDAS®; .
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.3: Contraindications Section 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reported AEs are consistent with the known safety profile of CANCIDAS® as noted in the SmPC. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 40 Risk Minimization Plan for Drug resistance

Safety Concern	Important identified risk
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that reports of drug resistance in adult and pediatric patients treated with caspofungin have been reported in clinical studies and in the postmarketing environment
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.1: Therapeutic indications Section 5.1 Pharmacodynamic properties
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reported AEs are consistent with the known safety profile of CANCIDAS® as noted in the SmPC. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 41 Risk Minimization Plan for Drug-drug interaction – Rifampin and other inducers of drug clearance

Safety Concern	Important identified risk
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that simultaneous use of caspofungin with rifampin or other inducers of drug clearance may decrease the levels of caspofungin in the blood. This may result in decrease in efficacy due to decreased levels of caspofungin and higher dosage of caspofungin may be required in adult and pediatric patients treated with caspofungin.t
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.2: Posology and method of administration Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reported AEs are consistent with the known safety profile of CANCIDAS® as noted in the SmPC. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 42 Risk Minimization Plan for Drug-drug interaction – Cyclosporin A

Safety Concern	Important identified risk
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that the simultaneous use of caspofungin with cyclosporin A may increase the levels of caspofungin in the blood. This may result in an increase of side effects such as increased liver enzymes related to caspofungin. in adult and pediatric patients treated with caspofungin
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.2: Posology and method of administration Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reported AEs are consistent with the known safety profile of CANCIDAS® as noted in the SmPC. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 43 Risk Minimization Plan for Drug-drug interaction – Tacrolimus

Safety Concern	Important identified risk
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that the simultaneous use of caspofungin with tacrolimus may decrease the levels of tacrolimus in the blood. This may result in decreased immunosuppression. in adult and pediatric patients treated with caspofungin
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.2: Posology and method of administration Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reported AEs are consistent with the known safety profile of CANCIDAS® as noted in the SmPC. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 44 Risk Minimization Plan for Exposure during pregnancy

Safety Concern	Missing information
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that there are limited to no data for CANCIDAS® in pregnant women and that it should only be used during pregnancy fi the expected benefit outweighs the possible risk to the pregnant woman and foetus.
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.6: Fertility, pregnancy and lactation Section 5.3 Preclinical safety data
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the Proposed Risk Minimization Measure(s)	Reports of exposure to CANCIDAS® during pregnancy from spontaneous reports will be reviewed and followed up for outcome. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

Table 45 Risk Minimization Plan for Additional data on the safety and effectiveness in neonates and infants < 3 months of age

Safety Concern	Missing information
Objective(s) of the Risk Minimization Measure(s)	The objective of this routine risk minimization is to inform healthcare providers and patient caregivers that data on the safety and effectiveness of CANCIDAS® in neonates and infants <3 months of age has not been established.
Routine Risk Minimization Measure(s)	**Text in SmPC** Section 4.2: Posology and method of administration – Posology - Pediatric patients
	Comment Not applicable
	Other Routine Risk Minimization Measure(s) No other routine risk mitigation measures are proposed
How Effectiveness of the Risk Minimization Measures for the Safety Concern Will be Measured	Routine safety surveillance and AE collection
Criteria for Judging the Success of the proposed risk minimization measure(s)	Reports of exposure to CANCIDAS® in patients <3 months of age, will be reviewed. Upon review of the data, appropriate measures will be taken if new information is obtained that alters the benefit-risk profile of CANCIDAS®
Planned Date(s) for Assessment	Ongoing
Results of Effectiveness Measurement	Not applicable
Impact of Risk Minimization	Not applicable
Comment	None

V.2 Risk Minimization Measure Failure

There are no risk minimization measures for caspofungin acetate that are judged to have failed.

V.2.1 Analysis of Risk Minimization Measure Failure

Not Applicable

V.2.2 Revised Proposal for Risk Minimization

Not Applicable

V.3 Summary Table of Risk Minimization Measures

Table 46 Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Important Identified Risks	
Increase in liver enzymes	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration – Special populations – Hepatic impairment Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 4.8: Undesirable effects	None
Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN	Communication via professional and patient product information – SmPC: Section 4.3: Contraindications Section 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects	None
Drug resistance	Communication via professional and patient product information – SmPC: Section 4.1: Therapeutic indications Section 5.1 Pharmacodynamic properties	None
Drug-drug interaction – Rifampin and other inducers of drug clearance	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities	None

Table 46 Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Drug-drug interaction – Cyclosporin A	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities	None
Drug-drug interaction – Tacrolimus	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities	None
	Important Potential Risks	
Important Potential Risk: **None**	N/A	N/A

Table 46 Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Missing Information	
Exposure during pregnancy	Communication via professional and patient product information – SmPC: Section 4.6: Fertility, pregnancy and lactation Section 5.3 Preclinical safety data	None
Additional data on the safety and effectiveness in neonates and infants < 3 months of age	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration – Posology - Pediatric patients	None

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for Summary Tables in the EPAR

VI.1.1 Summary Table of Safety Concerns

Table 47 Summary of Safety Concerns

Important identified risks	▪ Increase in liver enzymes ▪ Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN ▪ Drug resistance ▪ Drug-drug interaction: Rifampin and other inducers of drug clearance ▪ Drug-drug interaction: Cyclosporin A ▪ Drug-drug interaction: Tacrolimus
Important potential risks	▪ None
Missing information	▪ Exposure during pregnancy ▪ Additional data on the safety and effectiveness in neonates and infants < 3 months of age

VI.1.2 Table of Ongoing and Planned Studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post-authorization Efficacy Development Plan

Not applicable.

VI.I.4 Summary Table of Risk Minimization Measures

Table 48 Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Important Identified Risks	
Increase in liver enzymes	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration – Special populations – Hepatic impairment Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 4.8: Undesirable effects	None
Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN	Communication via professional and patient product information – SmPC: Section 4.3: Contraindications Section 4.4: Special warnings and precautions for use Section 4.8: Undesirable effects	None
Drug resistance	Communication via professional and patient product information – SmPC: Section 4.1: Therapeutic indications Section 5.1 Pharmacodynamic properties	None
Drug-drug interaction – Rifampin and other inducers of drug clearance	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities	None

Table 48 Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Drug-drug interaction – Cyclosporin A	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration Section 4.4: Special warnings and precautions for use Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities	None
Drug-drug interaction – Tacrolimus	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration Section 4.5: Interaction with other medicinal products and other forms of interaction Section 5.PHARMACOLOGICAL PROPERTIES Section 5.1: Pharmacodynamic properties Section 5.2: Pharmacokinetic properties Section 6.2: Incompatibilities	None
	Important Potential Risks	
Important Potential Risk: **None**	N/A	N/A

Table 48 Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Missing Information	
Exposure during pregnancy	Communication via professional and patient product information – SmPC: Section 4.6: Fertility, pregnancy and lactation Section 5.3 Preclinical safety data	None
Additional data on the safety and effectiveness in neonates and infants < 3 months of age	Communication via professional and patient product information – SmPC: Section 4.2: Posology and method of administration – Posology - Pediatric patients	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Indication: Invasive Aspergillosis

Invasive aspergillosis is a serious and often deadly infection of the lungs that can spread to the brain, skin, and bone. This infection is rare and occurs mostly in patients whose immune system is very weak and cannot fight infections, such as people who have had an organ or a stem cell transplant. [Ref. 5.4: 00W8W0].

Indication: Invasive Candidiasis

Invasive candidiasis occurs when *Candida* enters the blood and can then spread throughout the body. The disease is rare and mostly occurs in hospitalized patients. [Ref. 5.4: 04T70M, 00W895].

Indication: Empirical treatment of presumed fungal infections (such as Candida and Aspergillus spp.) in febrile, neutropenic adult patients.

As diagnostic tests for confirming type of fungal infection have imperfect precision and can take time, patients must often be treated based upon presumed fungal infection.

Indication: Oropharyngeal Candidiasis

Oropharyngeal candidiasis (OPC) is fungal infection that affects the mouth and throat-. OPC is rare and mostly affects people whose immune system is very weak and cannot fight

infections, such as people with cancer or HIV or other people who are whose immune systems are very weak because of their disease or disease treatments.

VI.2.2 Summary of Treatment Benefits

Prophylaxis of Invasive Fungal Infections

The standard for the prophylaxis (prevention) of invasive fungal infections involves liposomal amphotericin B, echinocandins (micafungin), fluconazole, and voriconazole. CANCIDAS® is used for the prophylaxis of invasive fungal infections in high risk patients. The main studies of CANCIDAS® for the prophylaxis of invasive fungal infections showed that in 1,111 subjects, who had fever or neutropenia at study entry (N=1095), the proportion (%) of patients with no documented breakthrough fungal infection was 527/556 (94.8%) with CANCIDAS® compared to 515/539 (95.5%) in patients treated with AmBisome (amphotericin B).

Invasive Aspergillosis

Voriconazole is the first-line treatment for invasive aspergillosis. In individuals who cannot tolerate or respond to voriconazole, other treatment options include the following: itraconazole, lipid amphotericin B formulations, CANCIDAS® (caspofungin acetate), micafungin and posaconazole.

The main studies of CANCIDAS® for the treatment of invasive aspergillosis showed that the response rate was 41% (26/63) of patients receiving at least one dose of CANCIDAS® had a favorable response.

Invasive Candidiasis

Per recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, echinocandins (caspofungin, anidulafungin, micafungin) are the first-line treatment for candidiasis. Additionally, Infectious Diseases Society of America (IDSA) guidelines note that echinocandins are the preferred treatment for unstable patients, patients receiving prior azole prophylaxis, and patients with documented *C. glabrata* or *C. krusei* infections. Azoles (fluconazole, voriconazole and posaconazole) are also used to treat candidiasis infection. Finally, Amphotericin B is another treatment option, and has been used for decades to treat candidiasis infection, but is associated with significant nephrotoxicity. At this time, antifungal prophylaxis should be limited to patients with gastrointestinal anastomotic leakage, patients undergoing transplantation of the pancreas or the small bowel, selected patients undergoing liver transplantation at high risk for candidiasis and extremely low-birthweight neonates in settings with high incidence of neonatal candidiasis. In a 239 subject study CANCIDAS® (caspofungin acetate) [(67/92 (72.8%)] was comparable to amphotericin B [63/94 (67.0%)] in the treatment of candidemia with favourable outcomes.

Oropharyngeal Candidiasis

Clotrimazole troches and nystatin suspension usually provide effective treatment. If infections do not respond to these treatments, systemic antifungals may be necessary. The options for systemic antifungals include: fluconazole, miconazole itraconazole, and posaconazole. In infants and children, nystatin is less effective than the azoles. In a 175 subject adult study, CANCIDAS® (caspofungin acetate)[66/81 (81.5%)] was comparable to fluconazole [80/94 (85.1%)] in the treatment of esophageal candidiasis with favourable outcomes.

VI.2.3 Unknowns Relating to Treatment Benefits

There are no or limited data for CANCIDAS® in pregnant/breastfeeding women and in infants <3 months of age.

VI.2.4 Summary of Safety Concerns

Table 49 and Table 51 provide information on the important identified risks and missing information for CANCIDAS®. Important identified risks are safety issues or undesirable effects for which there is adequate evidence of an association with the use of this medicine. Missing information is important information about the safety of a medicine which is not available at the time of submission of a particular Risk Management Plan. Some examples of missing information include patient populations not studied in clinical trials (e.g. pregnant women, young infants).

Important Identified Risks

Table 49 Summary of Important Identified Risks

Risk	What is Known	Preventability
Increased liver enzymes	The target population would be treated with another antifungal if not treated with CANCIDAS® thus the background rates in the population are considered to be rates in those treated with other antifungal agents. Hepatic effects (elevated ALT and/or AST) have been noted during treatment with other antifungal agents along with the concomitant use of CANCIDAS® with cyclosporine A.	There are no clear measures to prevent the elevations in liver function tests following the administration of CANCIDAS®. Specifically, patients receiving concomitant CANCIDAS® and cyclosporine A should have close monitoring of liver transaminase enzymes. In all other patients who develop transaminase elevations while on CANCIDAS® therapy, consideration should be given towards monitoring for a worsening in transaminase elevations or the development of clinical evidence of hepatic dysfunction. In the event of these events, the patients should be evaluated for the risk/benefit of continuing CANCIDAS® therapy.

Table 49 Summary of Important Identified Risks

Risk	What is Known	Preventability
Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN	Infusion-related reactions associated with polyenes may not necessarily be hypersensitivity reactions that are histamine-related, but these infusion-related events are routinely associated with findings similar to those seen with histamine-related events. SJS/TEN are type IV hypersensitivity reactions which is a type of cell-mediated response. This delayed type of hypersensitivity reaction occurs when the helper T cells are activated by an antigen. If the antigen is presented a second time, the memory cells will cause an inflammatory response which can ultimately lead to tissue damage. The immune reaction can be triggered by medications and infections.	CANCIDAS® is a lipopeptide that fits into the category of basic polypeptides that can effectively cause hypersensitivity by histamine release from mast cells. In nonclinical safety assessment studies in rats and monkeys, rapid intravenous infusion was shown to cause physical signs related to histamine release. Preadministration of anti-histamine agents (e.g., cyproheptadine) eliminated or significantly curtailed the development of these events, thereby helping to confirm the histamine-mediated mechanism of action. Importantly, the prolongation of the infusion time also improved these findings. SJS/TEN are very rare events often associated with medications or infections and primary prevention can be difficult since it is challenging to predict who will experience SJS/TEN. There can be a genetic predisposition to these events and patients with a potential predisposition should inform their medical professional before initiation of any medications. For patients who experience SJS/TEN, it is generally recommended to avoid rechallenge with a medication associated with the SJS/TEN event.
Drug resistance	Over time, fungi may not be killed by treatment with one or more antifungals, so these antifungals become less effective in treating fungal infections. This could lead to a serious situation if a serious fungal infection does not respond to CANCIDAS®.	The only active measures to prevent the development of resistance with CANCIDAS® would be to administer CANCIDAS® at the dose interval and duration described in the current SmPC. Less frequent daily maintenance dosages

Table 49 Summary of Important Identified Risks

Risk	What is Known	Preventability
		(i.e., <50 mg) and less frequent dosing intervals (i.e., every other day) should be avoided.
Drug-drug interaction – Rifampin and other inducers of drug clearance	The simultaneous use of caspofungin with rifampin or other inducers of drug clearance may decrease the levels of caspofungin in the blood. This may result in decrease in efficacy due to decreased levels of caspofungin and higher dosage of caspofungin may be required.	Patients taking caspofungin should inform the treating doctor if they are taking rifampin or other inducers of drug clearance as higher dosage of caspofungin may be required.
Drug-drug interaction – Cyclosporin A	The simultaneous use of caspofungin with cyclosporin A may increase the levels of caspofungin in the blood. This may result in an increase of side effects such as increased liver enzymes related to caspofungin.	Patients taking caspofungin should inform the treating doctor if they are taking cyclosporin A as using both drugs simultaneously can cause increase in liver enzymes.
Drug-drug interaction – Tacrolimus	The simultaneous use of caspofungin with tacrolimus may decrease the levels of tacrolimus in the blood. This may result in decreased immunosuppression.	Patients taking caspofungin should inform the treating doctor if they are taking tacrolimus as an increase in tacrolimus dosage may be required.

Important Potential Risks

Table 50 Summary of Important Potential Risks

Risk	What is Known
None	N/A

Missing Information

Table 51 Summary of Missing Information

Missing Information	What is Known
Exposure during pregnancy	There are no or limited data for CANCIDAS® in pregnant women. CANCIDAS® should not be used during pregnancy unless the benefit to the woman outweighs the potential risk.
Additional data on the safety and effectiveness in neonates and infants < 3 months of age	Clinical trials for CANCIDAS® were in patients 12 months of age and older, no data is available in patients <3 months age.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and the Package Leaflet for CANCIDAS® can be found in the product's EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6 Planned Post-authorization Development Plan

VI.2.6.1 List of Studies in Post-authorization Development Plan

There are no studies in the post-authorization development plan for this medicine.

VI.2.6.2 Studies Which are a Condition of the Marketing Authorization

There are no studies in the post-authorization development plan for this medicine.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 52 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
1.0	**15-JAN-2008**	**Important identified risks:** - Increase in liver enzymes - Histamine-mediated allergic reactions - Drug resistance **Important Potential Risks:** None **Important Missing Information:** - Exposure during pregnancy - Additional data on the safety and effectiveness in neonates and infants < 3 months of age	Initial RMP to include identified risks and missing information. Routine risk minimization was applied for all risks and missing information
2.0	**25-AUG-2008**	No new important safety concerns were added in the scope of this update (version 2.0).	RMP update to include new data on the pharmacokinetics, safety and efficacy of caspofungin at three times the licensed daily maintenance dose (i.e., 150 mg daily) in adult patients.
3.0	**23-FEB-2018**	RMP was updated to add SJS/TEN to the previously approved identified risk of Histamine-mediated allergic reactions. **Important identified risks:** - Histamine-mediated allergic reactions including SJS/TEN	Reports of SJS/ TEN were identified during routine postmarketing safety surveillance. Routine risk minimization is proposed for this risk.
3.1	**26-MAR-2018**	SVI.2 Potential for Transmission of Infectious Agents	CMC update.
3.2	**08-MAY-2018**	**Important identified risk:** Hypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN	As noted under RMP version 3.0 update, SJS/ TEN were added to the RMP based on a confirmed safety signal identified through routine signal detection. In response to an agency request, the MAH has clarified the description of the important identified risk to encompasshypersensitivity reactions including histamine-mediated allergic reactions and SJS/TEN.

REFERENCES

[Ref. 5.4: 00W88Z] Almirante B, Rodríguez D, Park BJ, Cuenca-Estrella M, Planes AM, Almela M, et al. Epidemiology and predictors of mortality in cases of candida bloodstream infection: Results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2005;43(4):1829-35.

[Ref. 5.4: 00W890] Asmundsdóttir LR, Erlendsdóttir H, Gottfredsson M. Increasing incidence of candidemia: Results from a 20-year nationwide study in Iceland. J Clin Microbiol 2002;40(9):3489-92.

[Ref. 5.4: 00W892] Bille J, Marchetti O, Calandra T. Changing face of health-care associated fungal infections. Curr Opin Infect Dis 2005;18:314-9.

[Ref. 5.4: 00W895] Clark TA, Hajjeh RA. Recent trends in the epidemiology of invasive mycoses. Curr Opin Infect Dis 2002;15:569-74.

[Ref. 5.4: 00W896] Cornet M, Fleury L, Maslo C, Bernard J-F, Brücker G. Epidemiology of invasive aspergillosis in France: A six-year multicentric survey in the Greater Paris area. J Hosp Infect 2002;51:288-96.

[Ref. 5.4: 00W898] Fidel Jr PL. Candida-host interactions in HIV disease: Relationships in oropharyngeal candidiasis. Adv Dent Res 2006;19:80-4.

[Ref. 5.4: 00W8H4] Gordon SM, Avery RK. Aspergillosis in lung transplantation: Incidence, risk factors, and prophylactic strategies. Transpl Infect Dis 2001;3:161-7.

[Ref. 5.4: 00W8H5] Hobson RP. The global epidemiology of invasive candida infections - is the tide turning? J Hosp Infect 2003;55:159-68.

[Ref. 5.4: 00W8J6] Pankhurst C. Oropharyngeal candidiasis: Search date October 2001. Clin Evid 2002;7:1248-62.

[Ref. 5.4: 00W8J8] Poikonen E, Lyytikäinen O, Anttila V-J, Ruutu P. Candidemia in Finland, 1995-1999. Emerg Infect Dis 2003;9(8):985-90.

[Ref. 5.4: 00W8J9] Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 2005;56(Suppl S1):i5-i11.

[Ref. 5.4: 00W8W0] Singh N, Paterson DL. Aspergillus infections in transplant recipients. Clin Microbiol Rev 2005;18(1):44-69.

[Ref. 5.4: 00W8W3] Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP, The National Nosocomial Infections Surveillance System Hospitals. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999. Clin Infect Dis 2002;35:627-30.

[Ref. 5.4: 00W9WX] Tortorano AM, Caspani L, Rigoni AL, Biraghi E, Sicignano A, Viviani MA. Candidosis in the intensive care unit: A 20-year survey. J Hosp Infect 2004;57:8-13.

[Ref. 5.4: 03P4R0] Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. N Engl J Med 1994;331(20):1325-30.

[Ref. 5.4: 03PBJD] Rex JH, Walsh TJ, Sobel JD, Filler SG, Pappas PG, Dismukes WE, et al. Practice guidelines for the treatment of candidiasis. Clin Infect Dis 2000;30:662-78.

[Ref. 5.4: 03PH5K] Mora-Duarte J, Betts R, Rotstein mC, Colombo AL, Thompson-Moya J, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347(25):2020-9.

[Ref. 5.4: 03PLQV] Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003;36:1221-8.

[Ref. 5.4: 03PPGF] Sanz-Rodriguez C, Lopez-Duarte M, Jurado M, Lopez J, Arranz R, Cisneros J-M, et al. Safety of the concomitant use of caspofungin and cyclosporin A in patients with invasive fungal infections. Bone Marrow Transplant 2004:1-8. RDS (Unisysis) does not have access to this online journal

[Ref. 5.4: 03PS4H] Marr KA, Hachem R, Papanicolaou G, Somani J, Arduino JM, Lipka CJ, et al. Retrospective study of the hepatic safety profile of patients concomitantly treated with caspofungin and cyclosporin A. Transpl Infect Dis 2004;6:110-6.

[Ref. 5.4: 03QG04] Package Circular: AmBisome®(amphotericin B) liposome for injection: 2000.

[Ref. 5.4: 03QG3N] Espinel-Ingroff A. In vitro antifungal activities of anidulafungin and micafungin, licensed agents and the investigational triazole posaconazole as determined by NCCLS methods for 12,052 fungal isolates: review of the literature. Rev Iberoam Micol 2003;20:121-36.

[Ref. 5.4: 03QG3P] Cuenca-Estrella M, Rodriguez D, Almirante B, Morgan J, Planes AM, Almela M, et al. In vitro susceptibilities of bloodstream isolates of Candida species to six antifungal agents: results from a population-based active surveillance programme, Barcelona, Spain, 2002 2003. J Antimicrob Chemother 2005;55:194-9.

[Ref. 5.4: 03QKCY] Ostrosky-Zeichner L, Rex JH, Bennett J, Kullberg B-J. Deeply invasive candidiasis. Infect Dis Clin N Am 2002;16:821-35.

[Ref. 5.4: 03QKRK] Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356(24):2472-82.

[Ref. 5.4: 03QKRL] Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366:1435-42.

[Ref. 5.4: 03QKRM] Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369:1519-27.

[Ref. 5.4: 03QKRN] Pappas PG, Rotstein CMF, Betts RF, Nucci M, Talwar D, De Waele JJ, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007;45(7):883-93.

[Ref. 5.4: 03R2S0] Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. CID 2001;32:358-66.

[Ref. 5.4: 043375] Pankhurst CL. Candidiasis (oropharyngeal). Clin Evid (Online). 2013 Nov 8;2013:1304.

[Ref. 5.4: 044763] Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014 Mar 27;370(13):1198-208.

[Ref. 5.4: 04S9XW] Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct 8;373(15):1445-56.

[Ref. 5.4: 04SXF4] Enoch DA, Ludlam HA, Brown NM. Invasive fungal infections: a review of epidemiology and management options. J Med Microbiol. 2006 Jul;55(Pt 7):809-18.

[Ref. 5.4: 04T5S3] Gradel KO, Schonheyder HC, Arpi M, Knudsen JD, Ostergaard C, Sogaard M. The Danish collaborative bacteraemia network (DACOBAN) database. Clin Epidemiol. 2014 Sep 18;6:301-8.

[Ref. 5.4: 04T70M] Cleveland AA, Harrison LH, Farley MM, Hollick R, Stein B, Chiller TM, et al. Declining incidence of candidemia and the shifting epidemiology of candida resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PLoS One. 2015 Mar 30;10(3):e0120452.

[Ref. 5.4: 04T94R] Frey N, Jossi J, Bodmer M, Bircher A, Jick SS, Meier CR, et al. The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK. J Invest Dermatol. 2017 Jun;137(6):1240-1247.

[Ref. 5.4: 04T94S] Rehmus WE. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Kenilworth: Merck Sharp & Dohme Corp ; 2017. 3p.

[Ref. 5.4: 04T94V] Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, et al. Incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Nationwide Population-Based Study Using National Health Insurance Database in Korea. PLoS One. 2016 Nov 11;11(11):e0165933.

[Ref. 5.4: 04TMSW] Nishimoto M, Koh H, Tokuwame A, Makuuchi Y, Kuno M, Takakuwa T, et al. Drug interactions and safety profiles with concomitant use of caspofungin and calcineurin inhibitors in allogeneic haematopoietic cell transplantation. Br J Clin Pharmacol. 2017 Sep;83(9):2000-7.

[Ref. 5.4: 04TMT7] Saner F, Gensicke J, Rath P, Fruhauf N, Gu Y, Paul A, et al. Safety profile of concomitant use of caspofungin and cyclosporine or tacrolimus in liver transplant patients. Infection. 2006 Dec;34(6):328-32.

[Ref. 5.4: 04TV6V] Groetzner J, Kaczmarek I, Wittwer T, Strauch J, Meiser B, Wahlers T, et al. Caspofungin as first-line therapy for the treatment of invasive aspergillosis after thoracic organ transplantation. J Heart Lung Transplant. 2008 Jan;27(1):1-6.

ANNEXES

ANNEX 1 INTERFACE BETWEEN RMP AND EUDRAVIGILANCE / EPITT

The EU-RMP Annex 1: Interface Between the EU-RMP and EudraVigilance / EPITT, reflecting the final, agreed version of this EU-RMP, will be submitted within 30 calendar days after the publication of the European Commission (EC) Decision (for new marketing authorizations) or 30 calendar days after the receipt of the CHMP Opinion (for all other updates to the EU-RMP). This EU-RMP Annex will be prepared in the form of an electronic file and submitted to the Agency via EudraLink.

ANNEX 2 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) AND PACKAGE LEAFLET

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 50 mg powder for concentrate for solution for infusion
CANCIDAS 70 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CANCIDAS 50 mg powder for concentrate for solution for infusion
Each vial contains 50 mg caspofungin (as acetate).

Excipients with known effect:
Each 50 mg vial contains 35.7 mg of sucrose.

CANCIDAS 70 mg powder for concentrate for solution for infusion
Each vial contains 70 mg caspofungin (as acetate).

Excipients with known effect
Each 70 mg vial contains 50.0 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Before reconstitution, the powder is a white to off-white-compact, powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive candidiasis in adult or paediatric patients.
- Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropaenic adult or paediatric patients.

4.2 Posology and method of administration

Caspofungin should be initiated by a physician experienced in the management of invasive fungal infections.

Posology

Adult patients
A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, caspofungin 70 mg daily is recommended (see section 5.2). No dosage adjustment is necessary based on gender or race (see section 5.2).

Paediatric patients (12 months to 17 years)
In paediatric patients (12 months to 17 years of age), dosing should be based on the patient's body surface area (see Instructions for Use in Paediatric Patients, Mosteller[1] Formula). For all indications, a single 70-mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). If the 50-mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg).

The safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age. Caution is advised when treating this age group. Limited data suggest that caspofungin at 25 mg/m^2 daily in neonates and infants (less than 3 months of age) and 50 mg/m^2 daily in young children (3 to 11 months of age) can be considered (see section 5.2).

Duration of treatment
Duration of empirical therapy should be based on the patient's clinical response. Therapy should be continued until up to 72 hours after resolution of neutropaenia (ANC≥500). Patients found to have a fungal infection should be treated for a minimum of 14 days and treatment should continue for at least 7 days after both neutropaenia and clinical symptoms are resolved.

Duration of treatment of invasive candidiasis should be based upon the patient's clinical and microbiological response. After signs and symptoms of invasive candidiasis have improved and cultures have become negative, a switch to oral antifungal therapy may be considered. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

Duration of treatment of invasive aspergillosis is determined on a case by case basis and should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. In general, treatment should continue for at least 7 days after resolution of symptoms.

The safety information on treatment durations longer than 4 weeks is limited. However, available data suggest that caspofungin continues to be well tolerated with longer courses of therapy (up to 162 days in adult patients and up to 87 days in paediatric patients).

Special populations
Elderly patients
In elderly patients (65 years of age or more), the area under the curve (AUC) is increased by approximately 30 %. However, no systematic dosage adjustment is required. There is limited treatment experience in patients 65 years of age and older (see section 5.2).

Renal impairment
No dosage adjustment is necessary based on renal impairment (see section 5.2).

Hepatic impairment
For adult patients with mild hepaticimpairment (Child-Pugh score 5 to 6), no dosage adjustment is needed. For adult patients with moderate hepatic impairment (Child-Pugh score 7 to 9), caspofungin 35 mg daily is recommended based upon pharmacokinetic data. An initial 70 mg loading dose should be administered on Day-1. There is no clinical experience in adult patients with severe hepatic impairment (Child-Pugh score greater than 9) and in paediatric patients with any degree of hepatic impairment (see section 4.4).

Co-administration with inducers of metabolic enzymes
Limited data suggest that an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered when co-administering caspofungin in adult patients with certain inducers of metabolic enzymes (see section 4.5). When caspofungin is co-administered to paediatric patients (12 months to 17 years of age) with these same inducers of metabolic enzymes (see

[1] Mosteller RD: Simplified Calculation of Body Surface Area. *N Engl J Med* 1987 Oct 22;317(17):1098 (letter)

section 4.5), a caspofungin dose of 70-mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

Method of administration
After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour. For reconstitution directions see section 6.6.

Both 70 mg and 50 mg vials are available.
Caspofungin should be given as a single daily infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Anaphylaxis has been reported during administration of caspofungin. If this occurs, caspofungin should be discontinued and appropriate treatment administered. Possibly histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment.

Limited data suggest that less common non-*Candida* yeasts and non-*Aspergillus* moulds are not covered by caspofungin. The efficacy of caspofungin against these fungal pathogens has not been established.

Concomitant use of caspofungin with cyclosporin has been evaluated in healthy adult volunteers and in adult patients. Some healthy adult volunteers who received two 3 mg/kg doses of cyclosporin with caspofungin showed transient increases in alanine transaminase (ALT) and aspartate transaminase (AST) of less than or equal to 3-fold the upper limit of normal (ULN) that resolved with discontinuation of the treatment. In a retrospective study of 40 patients treated during marketed use with caspofungin and cyclosporin for 1 to 290 days (median 17.5 days), no serious hepatic adverse reactions were noted. These data suggest that caspofungin can be used in patients receiving cyclosporin when the potential benefit outweighs the potential risk. Close monitoring of liver enzymes should be considered if caspofungin and cyclosporin are used concomitantly.

In adult patients with mild and moderate hepatic impairment, the AUC is increased about 20% and 75 %, respectively. A reduction of the daily dose to 35 mg is recommended for adults with moderate hepatic impairment. There is no clinical experience in adults with severe hepatic impairment or in paediatric patients with any degree of hepatic impairment. A higher exposure than in moderate hepatic impairment is expected and caspofungin should be used with caution in these patients (see sections 4.2 and 5.2).

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and paediatric patients treated with caspofungin. In some adult and paediatric patients with serious underlying conditions who were receiving multiple concomitant medications with caspofungin, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported; a causal relationship to caspofungin has not been established. Patients who develop abnormal liver function tests during caspofungin therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing caspofungin therapy should be re-evaluated.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance or sucrase–isomaltase insufficiency should not take this medicinal product (see section 2).

Cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post-marketing use of caspofungin. Caution should apply in patients with history of allergic skin reaction (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Studies *in vitro* show that caspofungin is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other substances. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes. However, caspofungin has been shown to interact with other medicinal products in pharmacological and clinical studies (see below).

In two clinical studies performed in healthy adult subjects, cyclosporin A (one 4 mg/kg dose or two 3 mg/kg doses 12 hours apart) increased the AUC of caspofungin by approximately 35 %. These AUC increases are probably due to reduced uptake of caspofungin by the liver. Caspofungin did not increase the plasma levels of cyclosporin. There were transient increases in liver ALT and AST of less than or equal to 3-fold the upper limit of normal (ULN) when caspofungin and cyclosporin were co-administered, that resolved with discontinuation of the medicinal products. In a retrospective study of 40 patients treated during marketed use with caspofungin and cyclosporin for 1 to 290 days (median 17.5 days), no serious hepatic adverse reactions were noted (see section 4.4). Close monitoring of liver enzymes should be considered if the two medicinal products are used concomitantly.

Caspofungin reduced the trough concentration of tacrolimus by 26 % in healthy adult volunteers. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are mandatory.

Clinical studies in healthy adult volunteers show that the pharmacokinetics of caspofungin are not altered to a clinically relevant extent by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus. Caspofungin did not influence the pharmacokinetics of amphotericin B, itraconazole, rifampicin or mycophenolate mofetil. Although safety data are limited it appears that no special precautions are needed when amphotericin B, itraconazole, nelfinavir or mycophenolate mofetil are co-administered with caspofungin.

Rifampicin caused a 60 % increase in AUC and 170 % increase in trough concentration of caspofungin on the first day of co-administration when both medicinal products were initiated together in healthy adult volunteers. Caspofungin trough levels gradually decreased upon repeated administration. After two weeks' administration rifampicin had limited effect on AUC, but trough levels were 30 % lower than in adult subjects who received caspofungin alone. The mechanism of interaction could possibly be due to an initial inhibition and subsequent induction of transport proteins. A similar effect could be expected for other medicinal products that induce metabolic enzymes. Limited data from population pharmacokinetics studies indicate that concomitant use of caspofungin with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered in adult patients (see section 4.2).

All adult drug-drug interaction studies described above were conducted at a 50 or 70 mg daily caspofungin dose. The interaction of higher doses of caspofungin with other medicinal products has not been formally studied.

In paediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with caspofungin may result in clinically meaningful reductions in caspofungin trough concentrations. This finding may indicate that paediatric patients will have similar reductions with inducers as seen in adults. When caspofungin is co-administered to paediatric patients (12 months to 17 years of age) with inducers of drug clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a caspofungin dose of 70-mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of caspofungin in pregnant women. Caspofungin should not be used during pregnancy unless clearly necessary. Animal studies have shown developmental toxicity (see section 5.3). Caspofungin has been shown to cross the placental barrier in animal studies.

Breast-feeding
It is unknown whether caspofungin is excreted in human milk. Available pharmacodynamic/ toxicological data in animals have shown excretion of caspofungin in milk. Women receiving caspofungin should not breast-feed.

Fertility
For caspofungin, there were no effects on fertility in studies conducted in male and female rats (see section 5.3). There are no clinical data for caspofungin to assess its impact on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Hypersensitivity reactions (anaphylaxis and possibly histamine-mediated adverse reactions) have been reported (see section 4.4).

Also reported in patients with invasive aspergillosis were pulmonary oedema, adult respiratory distress syndrome (ARDS), and radiographic infiltrates.

Adult patients
In clinical studies, 1,865 adult individuals received single or multiple doses of caspofungin: 564 febrile neutropaenic patients (empirical therapy study), 382 patients with invasive candidiasis, 228 patients with invasive aspergillosis, 297 patients with localised *Candida* infections, and 394 individuals enrolled in Phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation (including 39 allogeneic transplantations). In the studies involving patients with documented *Candida* infections, the majority of the patients with invasive *Candida* infections had serious underlying medical conditions (e.g., haematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the non-comparative *Aspergillus* study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications.

Phlebitis was a commonly reported local injection-site adverse reaction in all patient populations. Other local reactions included erythema, pain/tenderness, itching, discharge, and a burning sensation.

Reported clinical and laboratory abnormalities among all adults treated with caspofungin (total 1,780) were typically mild and rarely led to discontinuation.

Tabulated list of adverse reactions

The following adverse reactions were reported during clinical studies and/or post-marketing use:

System Organ Class	***Common (≥1/100 to <1/10)***	***Uncommon (≥1/1,000 to <1/100)***	***Not known (cannot be estimated from available data)***
Blood and	haemoglobin	anaemia, thrombocytopaenia,	

lymphatic system disorders	decreased, haematocrit decreased, white blood cell count decreased	coagulopathy, leukopaenia, eosinophil count increased, platelet count decreased, platelet count increased, lymphocyte count decreased, white blood cell count increased, neutrophil count decreased	
Metabolism and nutrition disorders	hypokalemia	fluid overload, hypomagnesaemia, anorexia, electrolyte imbalance, hyperglycaemia, hypocalcaemia, metabolic acidosis	
Psychiatric disorders		anxiety, disorientation, insomnia	
Nervous system disorders	headache	dizziness, dysgeusia, paraesthesia, somnolence, tremor, hypoaesthesia	
Eye disorders		ocular icterus, vision blurred, eyelid oedema, lacrimation increased	
Cardiac disorders		palpitations, tachycardia, arrhythmia, atrial fibrillation, cardiac failure congestive	
Vascular disorders	phlebitis	thrombophlebitis, flushing, hot flush, hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders	dyspnoea	nasal congestion, pharyngolaryngeal pain, tachypnoea, bronchospasm, cough, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing	
Gastrointestinal disorders	nausea, diarrhoea, vomiting	abdominal pain, abdominal pain upper, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia, flatulence	
Hepatobiliary disorders	elevated liver values (alanine aminotransferase, aspartate aminotranserase, blood alkaline phosphatase, bilirubin conjugated, blood bilirubin)	cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, hepatic function abnormal, hepatotoxicity, liver disorder, gamma-glutamyltransferase increased	
Skin and subcutaneous tissue disorders	rash, pruritus, erythema, hyperhidrosis	erythema multiforme, rash macular, rash maculo-papular, rash pruritic, urticaria, dermatitis allergic, pruritus generalised, rash erythematous, rash generalised, rash morbilliform, skin lesion	Toxic epidermal necrolysis and Stevens-Johnson syndrome (see section 4.4)
Musculoskeletal and connective tissue disorders	arthralgia	back pain, pain in extremity, bone pain, muscular weakness, myalgia	
Renal and urinary disorders		renal failure, renal failure acute	
General disorders and administration site conditions	pyrexia, chills, infusion-site pruritus	pain, catheter site pain, fatigue, feeling cold, feeling hot, infusion site erythema, infusion site induration, infusion site pain, infusion site swelling, injection site phlebitis, oedema peripheral, tenderness, chest discomfort, chest pain, face oedema, feeling of body temperature change, induration, infusion site extravasation,	

		infusion site irritation, infusion site phlebitis, infusion site rash, infusion site urticaria, injection site erythema, injection site oedema, injection site pain, injection site swelling, malaise, oedema	
Investigations	blood potassium decreased, blood albumin decreased	blood creatinine increased, red blood cells urine positive, protein total decreased, protein urine present, prothrombin time prolonged, prothrombin time shortened, blood sodium decreased, blood sodium increased, blood calcium decreased, blood calcium increased, blood chloride decreased, blood glucose increased, blood magnesium decreased, blood phosphorus decreased, blood phosphorus increased, blood urea increased, activated partial thromboplastin time prolonged, blood bicarbonate decreased, blood chloride increased, blood potassium increased, blood pressure increased, blood uric acid decreased, blood urine present, breath sounds abnormal, carbon dioxide decreased, immunosuppressant drug level increased, international normalised ratio increased, urinary casts, white blood cells urine positive, and pH urine increased.	

Caspofungin has also been evaluated at 150 mg daily (for up to 51 days) in 100 adult patients (see section 5.1). The study compared caspofungin at 50 mg daily (following a 70-mg loading dose on Day 1) versus 150 mg daily in the treatment of invasive candidiasis. In this group of patients, the safety of caspofungin at this higher dose appeared generally similar to patients receiving the 50-mg daily dose of caspofungin. The proportion of patients with a serious drug-related adverse reaction or a drug-related adverse reaction leading to caspofungin discontinuation was comparable in the 2 treatment groups.

Paediatric Patients
Data from 5 clinical studies completed in 171 paediatric patients suggest that the overall incidence of clinical adverse experiences (26.3%; 95% CI -19.9, 33.6) is not worse than reported for adults treated with caspofungin (43.1%; 95% CI -40.0, 46.2). However, paediatric patients probably have a different adverse event profile compared to adult patients. The most common drug-related clinical adverse experiences reported in paediatric patients treated with caspofungin were pyrexia (11.7%), rash (4.7%) and headache (2.9%).

Tabulated list of adverse reactions

The following adverse reactions were reported:

System Organ Class	***Very common (≥1/10)***	***Common (≥1/100 to <1/10)***
Blood and lymphatic system disorders		eosinophil count increased
Nervous system disorders		headache
Cardiac disorders		tachycardia
Vascular disorders		flushing, hypotension
Hepatobiliary disorders		elevated liver enzyme levels (AST, ALT)

Skin and subcutaneous tissue disorders		rash, pruritus
General disorders and administration site conditions	fever	chills, catheter site pain
Investigations		decreased potassium, hypomagnesemia, increased glucose, decreased phosphorus, and increased phosphorus

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Inadvertent administration of up to 400 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse reactions. Caspofungin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimycotics for systemic use, ATC Code: J02AX04

Mechanism of action
Caspofungin acetate is a semi-synthetic lipopeptide (echinocandin) compound synthesised from a fermentation product of *Glarea lozoyensis*. Caspofungin acetate inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of many filamentous fungi and yeast. Beta (1,3)-D-glucan is not present in mammalian cells.

Fungicidal activity with caspofungin has been demonstrated against *Candida* yeasts. Studies *in vitro* and *in vivo* demonstrate that exposure of *Aspergillus* to caspofungin results in lysis and death of hyphal apical tips and branch points where cell growth and division occur.

Pharmacodynamic effects
Caspofungin has *in vitro* activity against *Aspergillus* species (*Aspergillus fumigatus* [N = 75], *Aspergillus flavus* [N = 111], *Aspergillus niger* [N = 31], *Aspergillus nidulans* [N = 8], *Aspergillus terreus* [N = 52], and *Aspergillus candidus* [N = 3]). Caspofungin also has *in vitro* activity against *Candida* species (*Candida albicans* [N = 1,032], *Candida dubliniensis* [N = 100], *Candida glabrata* [N = 151], *Candida guilliermondii* [N = 67], *Candida kefyr* [N = 62], *Candida krusei* [N = 147], *Candida lipolytica* [N = 20], *Candida lusitaniae* [N = 80], *Candida parapsilosis* [N = 215], *Candida rugosa* [N = 1], and *Candida tropicalis* [N = 258]), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-flucytosine. Susceptibility testing was performed according to a modification of both the Clinical and Laboratory Standards Institute (CLSI, formerly known as the National Committee for Clinical Laboratory Standards [NCCLS]) method M38-A2 (for *Aspergillus* species) and method M27-A3 (for *Candida* species).

Standardised techniques for susceptibility testing have been established for yeasts by EUCAST. EUCAST breakpoints have not yet been established for caspofungin, due to significant inter-laboratory variation in MIC ranges for caspofungin. In lieu of breakpoints, Candida isolates that are susceptible to anidulafungin as well as micafungin should be considered susceptible to

caspofungin. Similarly, *C. parapsilosis* isolates intermediate to anidulafungin and micafungin can be regarded intermediate to caspofungin.

Mechanism of resistance
Isolates of Candida with reduced susceptibility to caspofungin have been identified in a small number of patients during treatment (MICs for caspofungin >2 mg/L (4- to 30-fold MIC increases) have been reported using standardized MIC testing techniques approved by the CLSI). The mechanism of resistance identified is FKS1 and/or FKS2 (for *C. glabrata*) gene mutations. These cases have been associated with poor clinical outcomes.

Development of *in vitro* resistance to caspofungin by *Aspergillus* species has been identified. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has been observed. The mechanism of resistance has not been established. The incidence of resistance to caspofungin by various clinical isolates of *Aspergillus* is rare. Caspofungin resistance in Candida has been observed but the incidence may differ by species or region.

Clinical efficacy and safety
Invasive Candidiasis in Adult Patients: Two hundred thirty-nine patients were enrolled in an initial study to compare caspofungin and amphotericin B for the treatment of invasive candidiasis. Twenty-four patients had neutropaenia. The most frequent diagnoses were bloodstream infections (candidaemia) (77 %, n = 186) and *Candida* peritonitis (8 %, n = 19); patients with *Candida* endocarditis, osteomyelitis, or meningitis were excluded from this study. Caspofungin 50 mg once daily was administered following a 70 mg loading dose, while amphotericin B was administered at 0.6 to 0.7 mg/kg/day to non-neutropaenic patients or 0.7 to 1.0 mg/kg/day to neutropaenic patients. The mean duration of intravenous therapy was 11.9 days, with a range of 1 to 28 days. A favourable response required both symptom resolution and microbiological clearance of the *Candida* infection. Two hundred twenty-four patients were included in the primary efficacy analysis (MITT analysis) of response at the end of IV study therapy; favourable response rates for the treatment of invasive candidiasis were comparable for caspofungin (73 % [80/109]) and amphotericin B (62 % [71/115]) [% difference 12.7 (95.6 % CI -0.7, 26.0)]. Among patients with candidaemia, favourable response rates at the end of IV study therapy were comparable for caspofungin (72 % [66/92]) and amphotericin B (63 % [59/94]) in the primary efficacy analysis (MITT analysis) [% difference 10.0 (95.0 % CI -4.5, 24.5)]. Data in patients with non-blood sites of infection were more limited. Favourable response rates in neutropaenic patients were 7/14 (50 %) in the caspofungin group and 4/10 (40 %) in the amphotericin B group. These limited data are supported by the outcome of the empirical therapy study.

In a second study, patients with invasive candidiasis received daily doses of caspofungin at 50 mg/day (following a 70-mg loading dose on Day 1) or caspofungin at 150 mg/day (see section 4.8). In this study, the caspofungin dose was administered over 2 hours (instead of the routine 1-hour administration). The study excluded patients with suspected *Candida* endocarditis, meningitis, or osteomyelitis. As this was a primary therapy study, patients who were refractory to prior antifungal agents were also excluded. The number of neutropenic patients enrolled in this study was also limited (8.0 %). Efficacy was a secondary endpoint in this study. Patients who met the entry criteria and received one or more doses of caspofungin study therapy were included in the efficacy analysis. The favourable overall response rates at the end of caspofungin therapy were similar in the 2 treatment groups: 72 % (73/102) and 78 % (74/95) for the caspofungin 50-mg and 150-mg treatment groups, respectively (difference 6.3 % [95 % CI -5.9, 18.4]).

Invasive Aspergillosis in Adult Patients: Sixty-nine adult patients (age 18-80) with invasive aspergillosis were enrolled in an open-label, non-comparative study to evaluate the safety, tolerability, and efficacy of caspofungin. Patients had to be either refractory to (disease progression or failure to improve with other antifungal therapies given for at least 7 days) (84 % of the enrolled patients) or intolerant of (16 % of enrolled patients) other standard antifungal therapies. Most patients had underlying conditions (haematologic malignancy [N = 24], allogeneic bone marrow transplant or stem cell transplant [N = 18], organ transplant [N = 8], solid tumour [N = 3], or other conditions [N = 10]). Stringent definitions, modelled after the Mycoses Study Group Criteria, were used for diagnosis of

invasive aspergillosis and for response to therapy (favourable response required clinically significant improvement in radiographs as well as in signs and symptoms). The mean duration of therapy was 33.7 days, with a range of 1 to 162 days. An independent expert panel determined that 41 % (26/63) of patients receiving at least one dose of caspofungin had a favourable response. For those patients who received more than 7 days of therapy with caspofungin, 50 % (26/52) had a favourable response. The favourable response rates for patients who were either refractory to or intolerant of previous therapies were 36 % (19/53) and 70 % (7/10), respectively. Although the doses of prior antifungal therapies in 5 patients enrolled as refractory were lower than those often administered for invasive aspergillosis, the favourable response rate during therapy with caspofungin was similar in these patients to that seen in the remaining refractory patients (2/5 versus 17/48, respectively). The response rates among patients with pulmonary disease and extrapulmonary disease were 47 % (21/45) and 28 % (5/18), respectively. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favourable response.

Empirical Therapy in Febrile, Neutropaenic Adult Patients: A total of 1,111 patients with persistent fever and neutropaenia were enrolled in a clinical study and treated with either caspofungin 50 mg once daily following a 70 mg loading dose or liposomal amphotericin B 3.0 mg/kg/day. Eligible patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation, and presented with neutropaenia (<500 cells/mm^3 for 96 hours) and fever (>38.0°C) not responding to ≥96 hours of parenteral antibacterial therapy. Patients were to be treated until up to 72 hours after resolution of neutropaenia, with a maximum duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated after 5 days of therapy, the dosage of study drug could be increased to 70 mg/day of caspofungin (13.3 % of patients treated) or to 5.0 mg/kg/day of liposomal amphotericin B (14.3 % of patients treated). There were 1,095 patients included in the primary Modified Intention-To-Treat (MITT) efficacy analysis of overall favourable response; caspofungin (33.9 %) was as effective as liposomal amphotericin B (33.7 %) [% difference 0.2 (95.2 % CI –5.6, 6.0)]. An overall favourable response required meeting each of 5 criteria: (1) successful treatment of any baseline fungal infection (caspofungin 51.9 % [14/27], liposomal amphotericin B 25.9 % [7/27]), (2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment (caspofungin 94.8 % [527/556], liposomal amphotericin B 95.5 % [515/539]), (3) survival for 7 days after completion of study therapy (caspofungin 92.6 % [515/556], liposomal amphotericin B 89.2 % [481/539]), (4) no discontinuation from the study drug because of drug-related toxicity or lack of efficacy (caspofungin 89.7 % [499/556], liposomal amphotericin B 85.5 % [461/539]), and (5) resolution of fever during the period of neutropaenia (caspofungin 41.2 % [229/556], liposomal amphotericin B 41.4 % [223/539]). Response rates to caspofungin and liposomal amphotericin B for baseline infections caused by *Aspergillus* species were, respectively, 41.7 % (5/12) and 8.3 % (1/12), and by *Candida* species were 66.7 % (8/12) and 41.7 % (5/12). Patients in the caspofungin group experienced breakthrough infections due to the following uncommon yeasts and moulds: *Trichosporon* species (1), *Fusarium* species (1), *Mucor* species (1), and *Rhizopus* species (1).

Paediatric population

The safety and efficacy of caspofungin was evaluated in paediatric patients 3 months to 17 years of age in two prospective, multicentre clinical trials. The study design, diagnostic criteria, and criteria for efficacy assessment were similar to the corresponding studies in adult patients (see section 5.1).

The first study, which enrolled 82 patients between 2 to 17 years of age, was a randomized, double-blind study comparing caspofungin (50 mg/m^2 IV once daily following a 70-mg/m^2 loading dose on Day 1 [not to exceed 70 mg daily]) to liposomal amphotericin B (3 mg/kg IV daily) in a 2:1 treatment fashion (56 on caspofungin, 26 on liposomal amphotericin B) as empirical therapy in paediatric patients with persistent fever and neutropenia. The overall success rates in the MITT analysis results, adjusted by risk strata, were as follows: 46.6 % (26/56) for caspofungin and 32.2 % (8/25) for liposomal amphotericin B.

The second study was a prospective, open-label, non-comparative study estimating the safety and efficacy of caspofungin in paediatric patients (ages 6 months to 17 years) with invasive candidiasis,

oesophageal candidiasis, and invasive aspergillosis (as salvage therapy). Forty-nine patients were enrolled and received caspofungin at 50 mg/m^2 IV once daily following a 70-mg/m^2 loading dose on Day 1 (not to exceed 70 mg daily), of whom 48 were included in the MITT analysis. Of these, 37 had invasive candidiasis, 10 had invasive aspergillosis, and 1 patient had esophageal candidiasis. The favourable response rate, by indication, at the end of caspofungin therapy was as follows in the MITT analysis: 81 % (30/37) in invasive candidiasis, 50 % (5/10) in invasive aspergillosis, and 100 % (1/1) in oesophageal candidiasis.

5.2 Pharmacokinetic properties

Distribution
Caspofungin is extensively bound to albumin. The unbound fraction of caspofungin in plasma varies from 3.5 % in healthy volunteers to 7.6 % in patients with invasive candidiasis. Distribution plays the prominent role in caspofungin plasma pharmacokinetics and is the rate-controlling step in both the alpha- and beta-disposition phases. The distribution into tissues peaked at 1.5 to 2 days after dosing when 92 % of the dose was distributed into tissues. It is likely that only a small fraction of the caspofungin taken up into tissues later returns to plasma as parent compound. Therefore, elimination occurs in the absence of a distribution equilibrium, and a true estimate of the volume of distribution of caspofungin is currently impossible to obtain.

Biotransformation
Caspofungin undergoes spontaneous degradation to an open ring compound. Further metabolism involves peptide hydrolysis and N-acetylation. Two intermediate products, formed during the degradation of caspofungin to this open ring compound, form covalent adducts to plasma proteins resulting in a low-level, irreversible binding to plasma proteins.

In vitro studies show that caspofungin is not an inhibitor of cytochrome P450 enzymes 1A2, 2A6, 2C9, 2C19, 2D6 or 3A4. In clinical studies, caspofungin did not induce or inhibit the CYP3A4 metabolism of other medicinal products. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

Elimination
The elimination of caspofungin from plasma is slow with a clearance of 10-12 ml/min. Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour intravenous infusions. A short alpha-phase occurs immediately post-infusion, followed by a beta-phase with a half-life of 9 to 11 hours. An additional gamma-phase also occurs with a half-life of 45 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance.

Approximately 75 % of a radioactive dose was recovered during 27 days: 41 % in urine and 34 % in faeces. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration. Excretion is slow and the terminal half-life of radioactivity was 12 to 15 days. A small amount of caspofungin is excreted unchanged in urine (approximately 1.4 % of dose).

Caspofungin displays moderate non-linear pharmacokinetics with increased accumulation as the dose is increased, and a dose dependency in the time to reach steady state upon multiple-dose administration.

Special populations
Increased caspofungin exposure was seen in adult patients with renal impairment and mild liver impairment, in female subjects, and in the elderly. Generally the increase was modest and not large enough to warrant dosage adjustment. In adult patients with moderate liver impairment or in higher weight patients, a dosage adjustment may be necessary (see below).

Weight: Weight was found to influence caspofungin pharmacokinetics in the population pharmacokinetic analysis in adult candidiasis patients. The plasma concentrations decrease with increasing weight. The average exposure in an adult patient weighing 80 kg was predicted to be about 23 % lower than in an adult patient weighing 60 kg (see section 4.2).

Hepatic impairment: In adult patients with mild and moderate hepatic impairment, the AUC is increased about 20 and 75 %, respectively. There is no clinical experience in adult patients with severe hepatic impairment and in paediatric patients with any degree of hepatic impairment. In a multiple-dose study, a dose reduction of the daily dose to 35 mg in adult patients with moderate hepatic impairment has been shown to provide an AUC similar to that obtained in adult subjects with normal hepatic function receiving the standard regimen (see section 4.2).

Renal impairment: In a clinical study of single 70 mg doses, caspofungin pharmacokinetics were similar in adult volunteers with mild renal impairment (creatinine clearance 50 to 80 ml/min) and control subjects. Moderate (creatinine clearance 31 to 49 ml/min), advanced (creatinine clearance 5 to 30 ml/min), and end-stage (creatinine clearance <10 ml/min and dialysis dependent) renal impairment moderately increased caspofungin plasma concentrations after single-dose administration (range: 30 to 49 % for AUC). However, in adult patients with invasive candidiasis, oesophageal candidiasis, or invasive aspergillosis who received multiple daily doses of caspofungin 50 mg, there was no significant effect of mild to advanced renal impairment on caspofungin concentrations. No dosage adjustment is necessary for patients with renal impairment. Caspofungin is not dialysable, thus supplementary dosing is not required following haemodialysis.

Gender: Caspofungin plasma concentrations were on average 17-38 % higher in women than in men.

Elderly: A modest increase in AUC (28 %) and C_{24h} (32 %) was observed in elderly male subjects compared with young male subjects. In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients.

Race: Patient pharmacokinetic data indicated that no clinically significant differences in the pharmacokinetics of caspofungin were seen among Caucasians, Blacks, Hispanics, and Mestizos.

Paediatric Patients:
In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24\ hr}$ was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses >50 mg daily, and, in fact, 6 of 8 received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.

In children (ages 2 to 11 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24\ hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day.

In young children and toddlers (ages 12 to 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24\ hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg daily and to that in older children (2 to 11 years of age) receiving the 50 mg/m^2 daily dose.

Overall, the available pharmacokinetic, efficacy, and safety data are limited in patients 3 to 10 months of age. Pharmacokinetic data from one 10-month old child receiving the 50 mg/m^2 daily dose indicated an $AUC_{0\text{-}24\ hr}$ within the same range as that observed in older children and adults at the 50 mg/m^2 and the 50 mg dose, respectively, while in one 6-month old child receiving the 50 mg/m^2 dose, the $AUC_{0\text{-}24\ hr}$ was somewhat higher.

In neonates and infants (<3 months) receiving caspofungin at 25 mg/m^2 daily (corresponding mean daily dose of 2.1 mg/kg), caspofungin peak concentration ($C_{1\ hr}$) and caspofungin trough concentration ($C_{24\ hr}$) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, $C_{1\ hr}$ was comparable and $C_{24\ hr}$ modestly elevated (36 %) in these neonates and infants relative to adults. However, variability was seen in both $C_{1\ hr}$ (Day 4 geometric mean 11.73 µg/ml, range 2.63 to 22.05 µg/ml) and $C_{24\ hr}$ (Day 4 geometric mean 3.55 µg/ml, range 0.13 to 7.17 µg/ml). $AUC_{0\text{-}24\ hr}$ measurements were not performed in this study due to the sparse plasma

sampling. Of note, the efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

5.3 Preclinical safety data

Repeated dose toxicity studies in rats and monkeys using doses up to 7-8 mg/kg given intravenously showed injection site reactions in rats and monkeys, signs of histamine release in rats, and evidence of adverse effects directed at the liver in monkeys. Developmental toxicity studies in rats showed that caspofungin caused decreases in foetal body weights and an increase in the incidence of incomplete ossification of vertebra, sternebra, and skull bone at doses of 5 mg/kg that were coupled to adverse maternal effects such as signs of histamine release in pregnant rats. An increase in the incidence of cervical ribs was also noted. Caspofungin was negative in *in vitro* assays for potential genotoxicity as well as in the *in vivo* mouse bone marrow chromosomal test. No long-term studies in animals have been performed to evaluate the carcinogenic potential. For caspofungin, there were no effects on fertility in studies conducted in male and female rats up to 5 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Mannitol
Glacial acetic acid
Sodium hydroxide (to adjust the pH)

6.2 Incompatibilities

Do not mix with diluents containing glucose, as CANCIDAS is not stable in diluents containing glucose. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

Reconstituted concentrate: should be used immediately. Stability data have shown that the concentrate for solution for infusion can be stored for up to 24 hours when the vial is stored at 25°C or less and reconstituted with water for injection.

Diluted patient infusion solution: should be used immediately. Stability data have shown that the product can be used within 24 hours when stored at 25°C or less, or within 48 hours when the intravenous infusion bag (bottle) is stored refrigerated (2 to 8°C) and diluted with sodium chloride solution 9 mg/ml (0.9 %), 4.5 mg/ml (0.45 %), or 2.25 mg/ml (0.225 %) for infusion, or lactated Ringer's solution.

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

6.4 Special precautions for storage

Unopened vials: store in a refrigerator (2°C - 8°C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

CANCIDAS 50 mg powder for concentrate for solution for infusion
10 ml Type I glass vial with a grey butyl stopper and a plastic cap with a red aluminium band.

CANCIDAS 70 mg powder for concentrate for solution for infusion
10 ml Type I glass vial with a grey butyl stopper and a plastic cap with an orange aluminium band.

Supplied in packs of 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution of CANCIDAS
DO NOT USE ANY DILUENTS CONTAINING GLUCOSE, as CANCIDAS is not stable in diluents containing glucose. DO NOT MIX OR CO-INFUSE CANCIDAS WITH ANY OTHER MEDICINES, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products. Visually inspect the infusion solution for particulate matter or discolouration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CANCIDAS 50 mg powder for concentrate for solution for infusion

INSTRUCTIONS FOR USE IN ADULT PATIENTS

Step 1 Reconstitution of conventional vials
To reconstitute the powder, bring the vial to room temperature and aseptically add 10.5 ml of water for injection. The concentrations of the reconstituted vials will be 5.2 mg/ml.

The white to off-white compact lyophilised powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25°C.

Step 2 Addition of reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or has precipitated.

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
50 mg	10 ml	0.20 mg/ml	-
50 mg at reduced volume	10 ml	-	0.47 mg/ml
35 mg for moderate hepatic impairment (from one 50 mg vial)	7 ml	0.14 mg/ml	-

DOSE*	Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle	Standard preparation (reconstituted CANCIDAS added to 250 ml) final concentration	Reduced volume infusion (reconstituted CANCIDAS added to 100 ml) final concentration
35 mg for moderate hepatic impairment (from one 50 mg vial) at reduced volume	7 ml	-	0.34 mg/ml

* 10.5 ml should be used for reconstitution of all vials.

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric dosing
Before preparation of infusion, calculate the body surface area (BSA) of the patient using the following formula: (Mosteller Formula)

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ X\ Weight\ (kg)}{3600}}$$

Preparation of the 70 mg/m^2 infusion for paediatric patients >3 months of age (using a 50-mg vial)

1. Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 70 mg/m^2 = Loading Dose
   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 5.2 mg/ml.
4. Remove the volume of medicinal product equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation of the 50 mg/m^2 infusion for paediatric patients >3 months of age (using a 50-mg vial)

1. Determine the actual daily maintenance dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 50 mg/m^2 = Daily Maintenance Dose
   The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 5.2 mg/ml.
4. Remove the volume of medicinal product equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C

Preparation notes:

a. The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

b. Visually inspect the reconstituted solution for particulate matter or discolouration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

c. CANCIDAS is formulated to provide the full labeled vial dose (50 mg) when 10 ml is withdrawn from the vial.

CANCIDAS 70 mg powder for concentrate for solution for infusion

INSTRUCTIONS FOR USE IN ADULT PATIENTS

Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injection. The concentrations of the reconstituted vials will be: 7.2 mg/ml.

The white to off-white compact lyophilised powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25°C.

Step 2 Addition of reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or has precipitated.

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
70 mg	10 ml	0.28 mg/ml	Not Recommended
70 mg (from two 50 mg vials)**	14 ml	0.28 mg/ml	Not Recommended
35 mg for moderate hepatic impairment (from one 70 mg vial)	5 ml	0.14 mg/ml	0.34 mg/ml

* 10.5 ml should be used for reconstitution of all vials.
**If 70 mg vial is not available, the 70 mg dose can be prepared from two 50 mg vials.

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric dosing
Before preparation of infusion, calculate the body surface area (BSA) of the patient using the following formula: (Mosteller Formula)

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ X\ Weight\ (kg)}{3600}}$$

Preparation of the 70 mg/m^2 infusion for paediatric patients >3 months of age (using a 70-mg vial)

1. Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 70 mg/m^2 = Loading Dose
   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 7.2 mg/ml.
4. Remove the volume of medicinal product equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation of the 50 mg/m^2 infusion for paediatric patients >3 months of age (using a 70-mg vial)

1. Determine the actual daily maintenance dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 50 mg/m^2 = Daily Maintenance Dose
   The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 7.2 mg/ml.
4. Remove the volume of medicinal product equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation notes:

a. The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

b. Visually inspect the reconstituted solution for particulate matter or discolouration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

c. CANCIDAS is formulated to provide the full labelled vial dose (70 mg) when 10 ml is withdrawn from the vial.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/001
EU/1/01/196/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 October 2001.
Date of latest renewal: 07 September 2011.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme BV, Waarderweg 39, 2031 BN Haarlem, The Netherlands
or
Laboratories Merck Sharp & Dohme- Chibret, Route de Marsat-RIOM, 63963 Clermont-Ferrand Cedex 9, France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 50 mg powder for concentrate for solution for infusion
Caspofungin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 50 mg caspofungin.

3. LIST OF EXCIPIENTS

Sucrose, mannitol, glacial acetic acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CANCIDAS 50 mg powder for concentrate for solution for infusion
Caspofungin
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 70 mg powder for concentrate for solution for infusion
Caspofungin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 70 mg caspofungin.

3. LIST OF EXCIPIENTS

Sucrose, mannitol, glacial acetic acid, and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/003

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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

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NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CANCIDAS 70 mg powder for concentrate for solution for infusion
Caspofungin
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Cancidas 50 mg powder for concentrate for solution for infusion
Caspofungin

Read all of this leaflet carefully before you or your child are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cancidas is and what it is used for

What Cancidas is
Cancidas contains a medicine called caspofungin. This belongs to a group of medicines called anti-fungals.

What Cancidas is used for
Cancidas is used to treat the following infections in children, adolescents and adults:
- serious fungal infections in your tissues or organs (called 'invasive candidiasis'). This infection is caused by fungal (yeast) cells called Candida.
  People who might get this type of infection include those who have just had an operation or those whose immune systems are weak. Fever and chills that do not respond to an antibiotic are the most common signs of this type of infection.
- fungal infections in your nose, nasal sinuses or lungs (called 'invasive aspergillosis') if other anti-fungal treatments have not worked or have caused side effects. This infection is caused by a mould called Aspergillus.
  People who might get this type of infection include those having chemotherapy, those who have had a transplant and those whose immune systems are weak.
- suspected fungal infections if you have a fever and a low white cell count that have not improved on treatment with an antibiotic. People who are at risk of getting a fungal infection include those who have just had an operation or those whose immune systems are weak.

How Cancidas works
Cancidas makes fungal cells fragile and stops the fungus from growing properly. This stops the infection from spreading and gives the body's natural defences a chance to completely get rid of the infection.

2. What you need to know before you are given Cancidas

Do not use Cancidas

- -if you are allergic to caspofungin or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, nurse or pharmacist before you are given your medicine.

Warnings and precautions
Talk to your doctor, nurse or pharmacist before you are given Cancidas if:
- you are allergic to any other medicines
- you have ever had liver problems - you might need a different dose of this medicine
- you are already taking cyclosporin (used to help prevent organ transplant rejection or to suppress your immune system) - as your doctor may need to run extra blood tests during your treatment.
- if you have ever had any other medical problem.

If any of the above applies to you (or you are not sure), talk to your doctor, nurse or pharmacist before you are given Cancidas.

Cancidas may also cause Serious Cutaneous Adverse Reactions such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).

Other medicines and Cancidas
Please tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Cancidas can affect the way some other medicines work. Also some other medicines can affect the way Cancidas works.

Tell your doctor, nurse or pharmacist if you are taking any of the following medicines:
- cyclosporin or tacrolimus (used to help prevent organ transplant rejection or to suppress your immune system) as your doctor may need to run extra blood tests during your treatment
- some HIV medicines such as efavirenz or nevirapine
- phenytoin or carbamazepine (used for the treatment of seizures)
- dexamethasone (a steroid)
- rifampicin (an antibiotic).

If any of the above apply to you (or you are not sure), talk to your doctor, nurse or pharmacist before you are given Cancidas.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine, if you are pregnant or breast-feeding or think you are pregnant.
- Cancidas has not been studied in pregnant women. It should be used in pregnancy only if the potential benefit justifies the potential risk to the unborn baby.
- Women given Cancidas should not breast-feed.

Driving and using machines
There is no information to suggest that Cancidas affects your ability to drive or operate machinery.

Cancidas contains sucrose
Cancidas contains sucrose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor, nurse or pharmacist before you are given this medicine.

3. How to use Cancidas

Cancidas will always be prepared and given to you by a healthcare professional.
You will be given Cancidas:
- once each day
- by slow injection into a vein (intravenous infusion)
- over about 1 hour.

Your doctor will determine the duration of your treatment and how much Cancidas you will be given each day. Your doctor will monitor how well the medicine works for you. If you weigh more than 80 kg, you may need a different dose.

Children and adolescents
The dose for children and adolescents may differ from the adult dose.

If you have been given more Cancidas than you should
Your doctor will decide how much Cancidas you need and for how long each day. If you are worried that you may have been given too much Cancidas, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse straight away if you notice any of the following side effects – you may need urgent medical treatment:
- rash, itching, feeling warm, swelling of your face, lips or throat or difficulty breathing - you may be having a histamine reaction to the medicine.
- difficulty breathing with wheezing or a rash that gets worse - you may be having an allergic reaction to the medicine.
- cough, serious breathing difficulties - if you are an adult and have invasive aspergillosis you may be experiencing a serious respiratory problem that could result in respiratory failure.
- rash, skin peeling, mucous membrane sores, hives, large areas of peeling skin.

As with any prescription medicine, some side effects may be serious. Ask your doctor for more information.

Other side effects in adults include

Common: may affect up to 1 in 10 people:
- Decreased haemoglobin (decreased oxygen carrying substance in the blood), decreased white blood cells
- Decreased blood albumin (a type of protein) in your blood, decreased potassium or low potassium levels in the blood
- Headache
- Inflammation of the vein
- Shortness of breath
- Diarrhoea, nausea or vomiting
- Changes in some laboratory blood tests (including increased values of some liver tests)
- Itching, rash, skin redness or sweating more than usual
- Joint pain
- Chills, fever
- Itching at the injection site.

Uncommon: may affect up to 1 in 100 people:
- Changes in some laboratory blood tests (including disease of blood clotting, platelets, red blood cells and white blood cells)
- Loss of appetite, increase in amount of body fluid, imbalance of salt in the body, high sugar level in the blood, low calcium level in the blood, increase calcium level in the blood, low magnesium level in the blood, increase in acid level in the blood
- Disorientation, feeling nervous, being unable to sleep

- Feeling dizzy, decreased feeling or sensitivity (especially in the skin), shaking, feeling sleepy, change in the way things taste, tingling or numbness
- Blurred vision, increase in tears, swollen eyelid, yellowing of the whites of the eyes
- Sensation of fast or irregular heart beats, rapid heart beat, irregular heart beat, abnormal heart rhythm, heart failure
- Flushing, hot flush, high blood pressure, low blood pressure, redness along a vein which is extremely tender when touched
- Tightening of the bands of muscle around the airways resulting in wheezing or coughing, fast breathing rate, shortness of breath that wakes you up, shortage of oxygen in the blood, abnormal breath sounds, crackling sounds in the lungs, wheezing, nasal congestion, cough, throat pain
- Belly pain, upper belly pain, bloating, constipation, difficulty swallowing, dry mouth, indigestion, passing gas, stomach discomfort, swelling due to build-up of fluid around the belly
- Decreased flow of bile, enlarged liver, yellowing of the skin and/or whites of the eyes, liver injury caused by a drug or chemical, liver disorder
- Abnormal skin tissue, generalised itching, hives, rash of varying appearance, abnormal skin, red often itchy spots on your arms and legs and sometimes on the face and the rest of the body
- Back pain, pain in an arm or leg, bone pain, muscle pain, muscle weakness
- Loss of kidney function, sudden loss of kidney function
- Catheter site pain, injection site complaints (redness, hard lump, pain, swelling, irritation, rash, hives, leaking of fluid from the catheter into the tissue), inflammation of vein at injection site
- Increased blood pressure and alterations in some laboratory blood tests (including kidney electrolyte and clotting tests), increased levels of the medicines you are taking that weaken the immune system
- Chest discomfort, chest pain, feeling of body temperature change, generally feeling unwell, general pain, swelling of the face, swelling of the ankles, hands or feet, swelling, tenderness, feeling tired.

Side effects in children and adolescents

Very common: may affect more than 1 in 10 people:
- Fever

Common: may affect up to 1 in 10 people:
- Headache
- Fast heart beat
- Flushing, low blood pressure
- Changes in some laboratory blood tests (increased values of some liver tests)
- Itching, rash
- Catheter site pain
- Chills
- Changes in some laboratory blood tests.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cancidas

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial (the first two numbers are the month; the next four numbers are the year). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Once Cancidas has been prepared, it should be used straight away. This is because it does not contain any ingredients to stop the growth of bacteria. Only a trained healthcare professional who has read the complete directions should prepare the medicine (please see below "Instructions of how to reconstitute and dilute Cancidas").

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cancidas contains
- The active substance is caspofungin. Each vial of Cancidas contains 50 mg of caspofungin.
- The other ingredients are sucrose, mannitol, glacial acetic acid and sodium hydroxide (please see section 2. What you need to know before you are given Cancidas).

What Cancidas looks like and contents of the pack
Cancidas is a sterile, white to off-white compact powder.

Each pack contains one vial of powder.

Marketing Authorisation Holder and Manufacturer

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Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
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Waarderweg 39
2031 BN Haarlem
The Netherlands

or

Laboratories Merck Sharp & Dohme- Chibret
Route de Marsat-RIOM
63963 Clermont-Ferrand Cedex 9
France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

Instructions of how to reconstitute and dilute CANCIDAS:

Reconstitution of CANCIDAS
DO NOT USE ANY DILUENTS CONTAINING GLUCOSE as CANCIDAS is not stable in diluents containing glucose. DO NOT MIX OR CO-INFUSE CANCIDAS WITH ANY OTHER MEDICINES, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products. Visually inspect the infusion solution for particulate matter or discolouration.

INSTRUCTIONS FOR USE IN ADULT PATIENTS

Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injection. The concentrations of the reconstituted vials will be 5.2 mg/ml.

The white to off-white compact lyophilised powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25°C.

Step 2 Addition of reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or has precipitated.

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
50 mg	10 ml	0.20 mg/ml	-
50 mg at reduced volume	10 ml	-	0.47 mg/ml
35 mg for moderate hepatic impairment (from one 50 mg vial)	7 ml	0.14 mg/ml	-

DOSE*	Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle	Standard preparation (reconstituted CANCIDAS added to 250 ml) final concentration	Reduced volume infusion (reconstituted CANCIDAS added to 100 ml) final concentration
35 mg for moderate hepatic impairment (from one 50 mg vial) at reduced volume	7 ml	-	0.34 mg/ml

* 10.5 ml should be used for reconstitution of all vials

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric dosing

Before preparation of infusion, calculate the body surface area (BSA) of the patient using the following formula: (Mosteller[2] Formula)

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ X\ Weight\ (kg)}{3600}}$$

Preparation of the 70 mg/m^2 infusion for paediatric patients >3 months of age (using a 50-mg vial)

1. Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 70 mg/m^2 = Loading Dose
   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 5.2 mg/ml.
4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation of the 50 mg/m^2 infusion for paediatric patients >3 months of age (using a 50-mg vial)

1. Determine the actual daily maintenance dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 50 mg/m^2 = Daily Maintenance Dose
   The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 5.2 mg/ml.
4. Remove the volume of medicine equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers

[2] Mosteller RD: Simplified Calculation of Body Surface Area. *N Engl J Med* 1987 Oct 22;317(17): 1098 (letter)

Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation notes:

a The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

b Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

c CANCIDAS is formulated to provide the full labelled vial dose (50 mg) when 10 ml is withdrawn from the vial.

Package Leaflet: Information for the user

Cancidas 70 mg powder for concentrate for solution for infusion
Caspofungin

Read all of this leaflet carefully before you or your child are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cancidas is and what it is used for

What Cancidas is
Cancidas contains a medicine called caspofungin. This belongs to a group of medicines called anti-fungals.

What Cancidas is used for
Cancidas is used to treat the following infections in children, adolescents and adults:
- serious fungal infections in your tissues or organs (called 'invasive candidiasis'). This infection is caused by fungal (yeast) cells called Candida.
  People who might get this type of infection include those who have just had an operation or those whose immune systems are weak. Fever and chills that do not respond to an antibiotic are the most common signs of this type of infection.
- fungal infections in your nose, nasal sinuses or lungs (called 'invasive aspergillosis') if other anti-fungal treatments have not worked or have caused side effects. This infection is caused by a mould called Aspergillus.
  People who might get this type of infection include those having chemotherapy, those who have had a transplant and those whose immune systems are weak.
- suspected fungal infections if you have a fever and a low white cell count that have not improved on treatment with an antibiotic. People who are at risk of getting a fungal infection include those who have just had an operation or those whose immune systems are weak.

How Cancidas works
Cancidas makes fungal cells fragile and stops the fungus from growing properly. This stops the infection from spreading and gives the body's natural defences a chance to completely get rid of the infection.

2. What you need to know before you are given Cancidas

Do not use Cancidas

- -if you are allergic to caspofungin or any of the other ingredients of this medicine (listed in Section 6).

If you are not sure, talk to your doctor, nurse or pharmacist before you are given your medicine.

Warnings and precautions
Talk to your doctor, nurse or pharmacist before you are given Cancidas if:
- you are allergic to any other medicines
- you have ever had liver problems - you might need a different dose of this medicine
- you are already taking cyclosporin (used to help prevent organ transplant rejection or to suppress your immune system) - as your doctor may need to run extra blood tests during your treatment.
- if you have ever had any other medical problem.

If any of the above applies to you (or you are not sure), talk to your doctor, nurse or pharmacist before you are given Cancidas.

Cancidas may also cause Serious Cutaneous Adverse Reactions such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).

Other medicines and Cancidas
Please tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Cancidas can affect the way some other medicines work. Also some other medicines can affect the way Cancidas works.

Tell your doctor, nurse or pharmacist if you are taking any of the following medicines:
- cyclosporin or tacrolimus (used to help prevent organ transplant rejection or to suppress your immune system) as your doctor may need to run extra blood tests during your treatment
- some HIV medicines such as efavirenz or nevirapine
- phenytoin or carbamazepine (used for the treatment of seizures)
- dexamethasone (a steroid)
- rifampicin (an antibiotic).

If any of the above apply to you (or you are not sure), talk to your doctor, nurse or pharmacist before you are given Cancidas.

Pregnancy and breastfeeding
Ask your doctor for advice before taking any medicine, if you are pregnant or breast-feeding or think you are pregnant.
- Cancidas has not been studied in pregnant women. It should be used in pregnancy only if the potential benefit justifies the potential risk to the unborn baby.
- Women given Cancidas should not breast-feed.

Driving and using machines
There is no information to suggest that Cancidas affects your ability to drive or operate machinery.

Cancidas contains sucrose
Cancidas contains sucrose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor, nurse or pharmacist before you are given this medicine.

3. How to use Cancidas

Cancidas will always be prepared and given to you by a healthcare professional.
You will be given Cancidas:
- once each day
- by slow injection into a vein (intravenous infusion)
- over about 1 hour.

Your doctor will determine the duration of your treatment and how much Cancidas you will be given each day. Your doctor will monitor how well the medicine works for you. If you weigh more than 80 kg, you may need a different dose.

Children and adolescents
The dose for children and adolescents may differ from the adult dose.

If you have been given more Cancidas than you should
Your doctor will decide how much Cancidas you need and for how long each day. If you are worried that you may have been given too much Cancidas, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse straight away if you notice any of the following side effects – you may need urgent medical treatment:
- rash, itching, feeling warm, swelling of your face, lips or throat or difficulty breathing - you may be having a histamine reaction to the medicine.
- difficulty breathing with wheezing or a rash that gets worse - you may be having an allergic reaction to the medicine.
- cough, serious breathing difficulties - if you are an adult and have invasive aspergillosis you may be experiencing a serious respiratory problem that could result in respiratory failure.
- rash, skin peeling, mucous membrane sores, hives, large areas of peeling skin.

As with any prescription medicine, some side effects may be serious. Ask your doctor for more information.

Other side effects in adults include

Common: may affect up to 1 in 10 people:
- Decreased haemoglobin (decreased oxygen carrying substance in the blood), decreased white blood cells
- Decreased blood albumin (a type of protein) in your blood, decreased potassium or low potassium levels in the blood
- Headache
- Inflammation of the vein
- Shortness of breath
- Diarrhoea, nausea or vomiting
- Changes in some laboratory blood tests (including increased values of some liver tests)
- Itching, rash, skin redness or sweating more than usual
- Joint pain
- Chills, fever
- Itching at the injection site.

Uncommon: may affect up to 1 in 100 people:
- Changes in some laboratory blood tests (including disease of blood clotting, platelets, red blood cells and white blood cells)
- Loss of appetite, increase in amount of body fluid, imbalance of salt in the body, high sugar level in the blood, low calcium level in the blood, increase calcium level in the blood, low magnesium level in the blood, increase in acid level in the blood
- Disorientation, feeling nervous, being unable to sleep

- Feeling dizzy, decreased feeling or sensitivity (especially in the skin), shaking, feeling sleepy, change in the way things taste, tingling or numbness
- Blurred vision, increase in tears, swollen eyelid, yellowing of the whites of the eyes
- Sensation of fast or irregular heart beats, rapid heart beat, irregular heart beat, abnormal heart rhythm, heart failure
- Flushing, hot flush, high blood pressure, low blood pressure, redness along a vein which is extremely tender when touched
- Tightening of the bands of muscle around the airways resulting in wheezing or coughing, fast breathing rate, shortness of breath that wakes you up, shortage of oxygen in the blood, abnormal breath sounds, crackling sounds in the lungs, wheezing, nasal congestion, cough, throat pain
- Belly pain, upper belly pain, bloating, constipation, difficulty swallowing, dry mouth, indigestion, passing gas, stomach discomfort, swelling due to build-up of fluid around the belly
- Decreased flow of bile, enlarged liver, yellowing of the skin and/or whites of the eyes, liver injury caused by a drug or chemical, liver disorder
- Abnormal skin tissue, generalised itching, hives, rash of varying appearance, abnormal skin, red often itchy spots on your arms and legs and sometimes on the face and the rest of the body
- Back pain, pain in an arm or leg, bone pain, muscle pain, muscle weakness
- Loss of kidney function, sudden loss of kidney function
- Catheter site pain, injection site complaints (redness, hard lump, pain, swelling, irritation, rash, hives, leaking of fluid from the catheter into the tissue), inflammation of vein at injection site
- Increased blood pressure and alterations in some laboratory blood tests (including kidney electrolyte and clotting tests), increased levels of the medicines you are taking that weaken the immune system
- Chest discomfort, chest pain, feeling of body temperature change, generally feeling unwell, general pain, swelling of the face, swelling of the ankles, hands or feet, swelling, tenderness, feeling tired.

Side effects in children and adolescents

Very common: may affect more than 1 in 10 people:
- Fever

Common: may affect up to 1 in 10 people:
- Headache
- Fast heart beat
- Flushing, low blood pressure
- Changes in some laboratory blood tests (increased values of some liver tests)
- Itching, rash
- Catheter site pain
- Chills
- Changes in some laboratory blood tests.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cancidas

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial (the first two numbers are the month; the next four numbers are the year). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Once Cancidas has been prepared, it should be used straight away. This is because it does not contain any ingredients to stop the growth of bacteria. Only a trained healthcare professional who has read the complete directions should prepare the medicine (please see below "Instructions of how to reconstitute and dilute Cancidas").

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cancidas contains
- The active substance is caspofungin. Each vial of Cancidas contains 70 mg of caspofungin.
- The other ingredients are sucrose, mannitol, glacial acetic acid and sodium hydroxide (please see section 2. What you need to know before you are given Cancidas).

What Cancidas looks like and contents of the pack
Cancidas is a sterile, white to off-white compact powder.

Each pack contains one vial of powder.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
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The Netherlands

or

Laboratories Merck Sharp & Dohme- Chibret
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France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

Instructions of how to reconstitute and dilute CANCIDAS:

Reconstitution of CANCIDAS
DO NOT USE ANY DILUENTS CONTAINING GLUCOSE as CANCIDAS is not stable in diluents containing glucose. DO NOT MIX OR CO-INFUSE CANCIDAS WITH ANY OTHER MEDICINES, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products. Visually inspect the infusion solution for particulate matter or discolouration.

INSTRUCTIONS FOR USE IN ADULT PATIENTS

Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injection. The concentrations of the reconstituted vials will be: 7.2 mg/ml.

The white to off-white compact lyophilised powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25°C.

Step 2 Addition of reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or has precipitated.

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
70 mg	10 ml	0.28 mg/ml	Not Recommended
70 mg (from two 50-mg vials)**	14 ml	0.28 mg/ml	Not Recommended
35 mg for moderate hepatic impairment (from one 70 mg vial)	5 ml	0.14 mg/ml	0.34 mg/ml

* 10.5 ml should be used for reconstitution of all vials
** If 70 mg vial is not available, the 70 mg dose can be prepared from two 50-mg vials

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric dosing

Before preparation of infusion, calculate the body surface area (BSA) of the patient using the following formula: (Mosteller[3] Formula)

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ X\ Weight\ (kg)}{3600}}$$

Preparation of the 70 mg/m^2 infusion for paediatric patients >3 months of age (using a 70-mg vial)

1. Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 70 mg/m^2 = Loading Dose
   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 7.2 mg/ml.
4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation of the 50 mg/m^2 infusion for paediatric patients >3 months of age (using a 70-mg vial)

1. Determine the actual daily maintenance dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 50 mg/m^2 = Daily Maintenance Dose
   The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3. Aseptically add 10.5 ml of water for injection.[a] This reconstituted solution may be stored for up to 24 hours at or below 25°C.[b] This will give a final caspofungin concentration in the vial of 7.2 mg/ml.
4. Remove the volume of medicine equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted CANCIDAS can be added to a reduced volume of 0.9 %, 0.45 %, or 0.225 % Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

Preparation notes:

a The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

b Visually inspect the reconstituted solution for particulate matter or discolouration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

c CANCIDAS is formulated to provide the full labelled vial dose (70 mg) when 10 ml is withdrawn from the vial.

[3] Mosteller RD: Simplified Calculation of Body Surface Area. *N Engl J Med* 1987 Oct 22;317(17): 1098 (letter)

ANNEX 3 WORLDWIDE MARKETING AUTHORIZATION BY COUNTRY (INCLUDING EEA)

Table 1 Licensing Status in the EEA

caspofungin acetate 50 mg

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Austria	Active	24-Oct-01	Feb 15, 2001 12:00:00 AM	CANCIDAS	
Belgium	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Bulgaria	Active	24-Oct-01		CANCIDAS	
Croatia	Active	24-Oct-01	Jul 1, 2013 12:00:00 AM	CANCIDAS	
Cyprus	Active	24-Oct-01	Oct 1, 2002 12:00:00 AM	CANCIDAS	
Czech Republic	Active	24-Oct-01	Nov 1, 2002 12:00:00 AM	CANCIDAS	
Denmark	Active	24-Oct-01	Aug 5, 2002 12:00:00 AM	CANCIDAS	
Estonia	Active	24-Oct-01	Nov 1, 2002 12:00:00 AM	CANCIDAS	
Finland	Active	24-Oct-01	Jul 9, 2002 12:00:00 AM	CANCIDAS	
France	Active	24-Oct-01	Jul 7, 2003 12:00:00 AM	CANCIDAS	
Germany	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	
Greece	Active	24-Oct-01	Jun 4, 2002 12:00:00 AM	CANCIDAS	
Hungary	Active	24-Oct-01	Jan 1, 2004 12:00:00 AM	CANCIDAS	
Iceland	Active	24-Oct-01	Feb 1, 2002 12:00:00 AM	CANCIDAS	
Ireland	Active	24-Oct-01	Oct 1, 2003 12:00:00 AM	CANCIDAS	
Italy	Active	24-Oct-01	Feb 13, 2003 12:00:00 AM	CANCIDAS	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Latvia	Active	24-Oct-01	Mar 20, 2003 12:00:00 AM	CANCIDAS	
Liechtenstein	Active	24-Oct-01		CANCIDAS	
Lithuania	Active	24-Oct-01	Jan 1, 2003 12:00:00 AM	CANCIDAS	
Luxembourg	Active	24-Oct-01	Oct 1, 2002 12:00:00 AM	CANCIDAS	
Malta	Active	24-Oct-01	Jan 1, 2003 12:00:00 AM	CANCIDAS	
Netherlands	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	
Norway	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Poland	Active	24-Oct-01	Oct 1, 2004 12:00:00 AM	CANCIDAS	
Portugal	Active	24-Oct-01	Sep 26, 2002 12:00:00 AM	CANCIDAS	
Romania	Active	24-Oct-01	Jun 25, 2002 12:00:00 AM	CANCIDAS	
Slovakia	Active	24-Oct-01	Dec 1, 2003 12:00:00 AM	CANCIDAS	
Slovenia	Active	24-Oct-01	Dec 1, 2001 12:00:00 AM	CANCIDAS	
Spain	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Sweden	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	Sweden
United Kingdom	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	United Kingdom

caspofungin acetate 70 mg

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Austria	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Belgium	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Bulgaria	Active	24-Oct-01	Aug 1, 2009 12:00:00 AM	CANCIDAS	
Croatia	Active	24-Oct-01	Jul 1, 2013 12:00:00 AM	CANCIDAS	
Cyprus	Active	24-Oct-01	Oct 1, 2002 12:00:00 AM	CANCIDAS	
Czech Republic	Active	24-Oct-01	Nov 1, 2002 12:00:00 AM	CANCIDAS	
Denmark	Active	24-Oct-01	Aug 5, 2002 12:00:00 AM	CANCIDAS	
Estonia	Active	24-Oct-01	Nov 1, 2002 12:00:00 AM	CANCIDAS	
Finland	Active	24-Oct-01	Jul 9, 2002 12:00:00 AM	CANCIDAS	
France	Active	24-Oct-01	Jul 7, 2003 12:00:00 AM	CANCIDAS	
Germany	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	
Greece	Active	24-Oct-01	Jun 27, 2002 12:00:00 AM	CANCIDAS	
Hungary	Active	24-Oct-01	Jan 1, 2004 12:00:00 AM	CANCIDAS	
Iceland	Active	24-Oct-01	Feb 1, 2002 12:00:00 AM	CANCIDAS	
Ireland	Active	24-Oct-01	Oct 1, 2003 12:00:00 AM	CANCIDAS	
Italy	Active	24-Oct-01	Feb 13, 2003 12:00:00 AM	CANCIDAS	
Latvia	Active	24-Oct-01	Mar 20, 2003 12:00:00 AM	CANCIDAS	
Liechtenstein	Active	24-Oct-01		CANCIDAS	
Lithuania	Active	24-Oct-01	Jan 1, 2003 12:00:00 AM	CANCIDAS	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Luxembourg	Active	24-Oct-01	Nov 1, 2002 12:00:00 AM	CANCIDAS	
Malta	Active	24-Oct-01	Jan 1, 2003 12:00:00 AM	CANCIDAS	
Netherlands	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	
Norway	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Poland	Active	24-Oct-01	Oct 1, 2004 12:00:00 AM	CANCIDAS	
Portugal	Active	24-Oct-01	Sep 26, 2002 12:00:00 AM	CANCIDAS	
Romania	Active	24-Oct-01	Jun 25, 2002 12:00:00 AM	CANCIDAS	
Slovakia	Active	24-Oct-01	Dec 1, 2003 12:00:00 AM	CANCIDAS	
Slovenia	Active	24-Oct-01	Dec 1, 2001 12:00:00 AM	CANCIDAS	
Spain	Active	24-Oct-01	Aug 1, 2002 12:00:00 AM	CANCIDAS	
Sweden	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	
United Kingdom	Active	24-Oct-01	Jul 1, 2002 12:00:00 AM	CANCIDAS	

Table 2 Licensing Status in the Rest of the World

caspofngin acetate 50 mg

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Algeria	Active	23-Jul-06		CANCIDAS	
Argentina	Active	24-Apr-01		CANCIDAS	
Aruba	Withdrawn	13-Feb-14		CANCIDAS INFUSION 50 MG	
Australia	Active	21-Aug-01		CANCIDAS	
Azerbaijan	Active	19-Feb-13		Cancidas	
Bahrain	Active	5-Mar-03		CANCIDAS	
Bangladesh	Active	4-Nov-15		CANCIDAS	
Belarus	Active	28-Oct-03		CANCIDAS	
Bosnia and Herzegovina	Active	27-Sep-04	Aug 1, 2008 12:00:00 AM	CANCIDAS	
Botswana	Active	17-Jul-14		CANCIDAS 50 mg	
Brazil	Active	7-May-01		CANCIDAS	
Brunei Darussalam	Active	28-Mar-12		CANCIDAS	
Canada	Active	19-Jul-01		CANCIDAS	
Chile	Active	30-Dec-02		CANCIDAS	
China	Active	27-Sep-17		CANCIDAS	
Colombia	Active	28-Jun-12		CANCIDAS	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Costa Rica	Active	22-May-01		CANCIDAS	
Curacao	Active	18-Sep-01	Sep 18, 2001 12:00:00 AM	CANCIDAS INFUSION 50MG	
Dominican Republic	Active	24-Jan-13		CANCIDAS	
Ecuador	Active	15-Jul-06		CANCIDAS	
Egypt	Active	8-Feb-12		CANCIDAS 50MG	
El Salvador	Active	29-Aug-01		CANCIDAS	
Ethiopia	Active	9-Jun-16		CANCIDAS 50MG	
Guatemala	Active	20-Jul-01		CANCIDAS	
Honduras	Active	27-Feb-02		CANCIDAS	
Hong Kong	Active	5-Jul-02	Aug 12, 2002 12:00:00 AM	CANCIDAS 50 MG/VIAL	
India	Active	4-Jul-06		CANCIDAS	
Indonesia	Withdrawn	20-Apr-17		CANCIDAS 50MG	
Iran, Islamic Republic of	Active	16-Jul-07		CANCIDAS	
Israel	Active	17-Dec-01		CANCIDAS 50 MG	
Jamaica	Active	27-Feb-02	Feb 18, 2002 12:00:00 AM	CANCIDAS INFUSION 50 mg	
Japan	Active	18-Jan-12		カンサイダス点滴静注用50mg（CANCIDAS for Intravenous Drip Infusion 50mg）	
Jordan	Active	3-Mar-03		CANCIDAS	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Kazakhstan	Active	29-Jan-10		CANCIDAS	
Kenya	Active	18-Dec-14		CANCIDAS 50 mg	
Korea, Republic of	Active	12-Dec-01		CANCIDAS	
Kuwait	Active	7-Oct-02		Cancidas 50mg	
Lebanon	Active	13-Mar-13		cancidas	
Macedonia, The Former Yugoslav Republic of	Active	27-Jan-06	Jan 1, 2010 12:00:00 AM	CANCIDAS	
Malaysia	Active	23-Mar-06		CANCIDAS INJECTION 50MG/VIAL	
Mexico	Active	14-Dec-00		CANCIDAS	
Moldova, Republic of	Active	28-Jul-14		CANCIDAS	
Montenegro	Active	25-Jul-11		CANCIDAS	
Namibia	Active	1-Mar-12		CANCIDAS 50 mg	
New Zealand	Active	4-Apr-02		CANCIDAS	
Nicaragua	Active	10-Oct-02		CANCIDAS	
Panama	Active	3-Dec-04		CANCIDAS	
Peru	Active	11-Apr-06		CANCIDAS 50 mg	
Philippines	Active	14-Feb-03		CANCIDAS	
Qatar	Active	1-Jun-03		CANCIDAS	
Russian Federation	Active	14-Apr-03		CANCIDAS	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Saudi Arabia	Active	19-Aug-03		CANCIDAS	
Serbia	Active	22-Sep-04		CANCIDAS	
Singapore	Active	10-Jan-02		CANCIDAS	
South Africa	Active	12-Nov-04		CANCIDAS 50 MG	
Switzerland	Active	2-Apr-02	Apr 2, 2001 12:00:00 AM	CANCIDAS	
Taiwan	Active	1-Jul-02		CANCIDAS	
Thailand	Active	12-Jun-12		CANCIDAS	
Trinidad and Tobago	Active	18-Dec-01		CANCIDAS INFUSION 50MG	
Tunisia	Active	18-Jul-07		CANCIDAS	
Turkey	Active	22-Sep-03		CANCIDAS 50 mg Lyophilised Powder For İnfusion	
Ukraine	Active	14-Mar-05		CANCIDAS	
United Arab Emirates	Active	14-Jan-03		Cancidas 50mg	
United States	Active	26-Jan-01		CANCIDAS	
Uruguay	Active	14-Oct-02		CANCIDAS	
Uzbekistan	Active	16-Aug-13		CANCIDAS	
Venezuela, Bolivarian Republic of	Active	21-Feb-02		CANCIDAS	
Viet Nam	Active	17-Jul-14		CANCIDAS	

caspofungin acetate 70 mg

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Algeria	Active	23-Jul-06		CANCIDAS	
Argentina	Active	24-Apr-01		CANCIDAS	
Aruba	Withdrawn	3-Apr-12		CANCIDAS INFUSION 70 MG	
Australia	Active	21-Aug-01		CANCIDAS	
Azerbaijan	Active	19-Feb-13		Cancidas	
Bahrain	Active	5-Mar-03		CANCIDAS	
Bangladesh	Active	4-Nov-15		CANCIDAS	
Belarus	Active	28-Oct-03		CANCIDAS	
Bosnia and Herzegovina	Active	27-Sep-04	Aug 1, 2008 12:00:00 AM	CANCIDAS	
Botswana	Active	17-Jul-14		CANCIDAS 70 mg	
Brazil	Active	7-May-01		CANCIDAS	
Brunei Darussalam	Active	30-Apr-12		Cancidas	
Canada	Active	26-Jan-01		CANCIDAS	
Chile	Active	30-Dec-02		CANCIDAS	
China	Active	27-Sep-17		CANCIDAS	
Colombia	Active	28-Jun-12		CANCIDAS	
Costa Rica	Active	13-Jul-01		CANCIDAS	
Curacao	Active	18-Sep-01	Sep 18, 2001 12:00:00 AM	CANCIDAS INFUSION 70MG	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Dominican Republic	Active	15-Jun-13	Aug 9, 2013 12:00:00 AM	CANCIDAS	
Ecuador	Active	15-Jul-06		CANCIDAS	
Egypt	Active	8-Feb-12		CANCIDAS 70MG	
El Salvador	Active	29-Aug-01		CANCIDAS	
Ethiopia	Active	9-Jun-16		CANCIDAS 70 MG	
Guatemala	Active	20-Jul-01		CANCIDAS	
Honduras	Active	18-Mar-02		CANCIDAS	
Hong Kong	Active	5-Jul-02	Aug 12, 2002 12:00:00 AM	CANCIDAS 70 MG	
India	Active	4-Jul-06		CANCIDAS	
Indonesia	Withdrawn	20-Apr-17		CANCIDAS 70 MG	
Iran, Islamic Republic of	Active	16-Jul-07		CANCIDAS	
Israel	Active	17-Dec-01		CANCIDAS 70MG	
Jamaica	Active	27-Feb-02		CANCIDAS INFUSION 70 mg	
Japan	Active	18-Jan-12		カンサイダス点滴静注用 70mg（CANCIDAS for Intravenous Drip Infusion 70mg）	
Jordan	Active	3-Mar-03		CANCIDAS	
Kazakhstan	Active	29-Jan-10		CANCIDAS	
Kenya	Active	18-Dec-14		CANCIDAS 70 mg	
Korea, Republic of	Active	12-Dec-01		CANCIDAS	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Kuwait	Active	7-Oct-02		Cancidas 70mg	
Lebanon	Active	13-Mar-13		cancidas	
Macedonia, The Former Yugoslav Republic of	Active	27-Jan-06	Jan 1, 2010 12:00:00 AM	CANCIDAS	
Malaysia	Active	23-Mar-06		CANCIDAS 70MG/VIAL	
Mexico	Active	14-Dec-00		CANCIDAS	
Moldova, Republic of	Active	28-Jul-14		CANCIDAS	
Montenegro	Active	25-Jul-11		CANCIDAS	
Namibia	Active	1-Mar-12		CANCIDAS 70 mg	
New Zealand	Active	4-Apr-02		CANCIDAS	
Nicaragua	Active	10-Oct-02		CANCIDAS	
Panama	Active	3-Dec-04		CANCIDAS	
Peru	Active	11-Apr-06		CANCIDAS 70 mg	
Philippines	Active	14-Feb-03		CANCIDAS	
Qatar	Active	1-Jun-03		CANCIDAS	
Russian Federation	Active	14-Apr-03		CANCIDAS	
Saudi Arabia	Active	20-Aug-03		CANCIDAS	
Serbia	Active	22-Sep-04		CANCIDAS	
Singapore	Active	10-Jan-02		CANCIDAS 70MG	
South Africa	Active	12-Nov-04		CANCIDAS 70 MG	

Country	Current License Status	Date of License Action	Date First Marketed in Country	Brand Name(s)	Comments
Switzerland	Active	2-Apr-02	Apr 2, 2001 12:00:00 AM	CANCIDAS	
Taiwan	Withdrawn	16-Aug-16		CANCIDAS	
Thailand	Active	12-Jun-12		CANCIDAS	
Trinidad and Tobago	Active	18-Dec-01		CANCIDAS INFUSION 70MG	
Tunisia	Active	18-Jul-07		CANCIDAS	
Turkey	Active	22-Sep-03		CANCIDAS 70 mg Lyophilised Powder For İnfusion	
Ukraine	Active	14-Mar-05		CANCIDAS	
United Arab Emirates	Active	14-Jan-03		Cancidas 70mg	
United States	Active	26-Jan-01		CANCIDAS	
Uruguay	Active	14-Oct-02		CANCIDAS	
Uzbekistan	Active	16-Aug-13		CANCIDAS	
Venezuela, Bolivarian Republic of	Active	21-Feb-02		CANCIDAS	
Viet Nam	Active	17-Jul-14		CANCIDAS	

ANNEX 4 SYNOPSIS OF ON-GOING AND COMPLETED CLINICAL TRIAL PROGRAM

Table 1 Summary of Ongoing and Completed Clinical Trial Program

Study	Description, Phase	Countries	Study Design	Planned / Actual Number of Patients	Duration of Follow-up	Estimated / Actual Completion Date
Main or pivotal studies						
Not Applicable						
Further safety / efficacy studies						
Not Applicable						
Studies in special populations						
MK-0991-064	Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age, Phase 2a	Romania South Africa Turkey Bulgaria Ukraine Brazil Columbia Mexico USA	Double-Blind, Randomized,	51	8 weeks	31-Aug-2018

ANNEX 5 SYNOPSIS OF ON-GOING AND COMPLETED PHARMACOEPIDEMIOLOGICAL STUDY PROGRAM

There are no ongoing / completed pharmcoepidemiological studies for caspofungin acetate.

ANNEX 6 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN CATEGORIES 1-3 OF THE SECTION "SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES" IN RMP PART III

Table 1 Overview of Included Protocols

Study Title	Protocol Status	Version of Protocol	Date of Protocol Version
none			

ANNEX 7 SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Not applicable

ANNEX 8 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

There are no proposed / ongoing post-authorization efficacy studies (PAES) for caspofungin acetate.

ANNEX 9 SYNOPSIS OF NEWLY AVAILABLE STUDY REPORTS FOR RMP PARTS III-IV

There are no newly-available study reports for studies in RMP Parts III-IV for caspofungin acetate.

ANNEX 10 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not applicable

ANNEX 11 MOCK-UP OF PROPOSED ADDITIONAL RISK MINIMIZATION MEASURES

Not applicable

ANNEX 12 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Table 1 Index of Included Material

Section	Title / Description
1	Literature Referenced in the Risk Management Plan

Section 1: Literature Referenced in the Risk Management Plan

The literature referenced in the Risk Management Plan (RMP) is provided as follows: the bibliographic information is provided in the List of References bibliographic sections of the RMP document. The List of References includes links to copies of the literature references, which are provided in Module 5.4.