VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Invasive candidiasis is a fungal infection that can occur when Candida yeasts enter the bloodstream. Once the fungus is in the bloodstream, it can spread to other parts of the body and cause infection.

Invasive candidiasis is extremely rare in people without risk factors, but it is the fourth most common cause of hospital-acquired bloodstream infections in the U.S. In the general population, the incidence is 8 to 10 cases per 100,000 people. A higher incidence has been observed among Blacks/African-Americans and babies less than one month old. It is estimated that between 5% and 20% of newborns that weigh less than 1000 grams (2.2 pounds) at birth develop invasive candidiasis.

According to the results of the SENTRY Antimicrobial Surveillance Program, 1,354 infection episodes related to Candida species were detected between 2008 and 2009 and 36.5% of these were community-acquired. Community-acquired candidemia was found to be significantly higher in North America (63.5%) than in Europe (22.4%).

Aspergillosis is the name given to a wide variety of diseases caused by infection by fungi of the genus Aspergillus. Invasive aspergillosis typically manifests as fever, cough, shortness of breath, sharp pain when breathing, and sometimes coughing up blood in patients with an abnormally low number of neutrophils (serving as the primary defence against infections by destroying bacteria in the blood)or with reduction of the immune system and its ability to fight infection.

The frequency of invasive aspergillosis reflects disease states and treatments that result in prolonged neutropenia and immunosuppression. Invasive aspergillosis is estimated to occur in 5-13% of recipients of bone marrow transplants, 5-25% of patients who have received heart or lung transplants, and 10-20% of patients who are receiving intensive chemotherapy for leukemia. Invasive aspergillosis is uncommon in individuals with a normal immune system.

VI.2.2 Summary of treatment benefits

Caspofungin is an antifungal drug. It is a member of a new class of antifungals termed the echinocandins. It works by inhibiting the enzyme (1→3)-β-D-glucan synthase and thereby disturbing the integrity of the fungal cell wall.

The choice of antifungal therapy for invasive candidiasis, including candidemia, depends upon a variety of factors including history of recent azole exposure; prevalence of different Candida species and current antifungal susceptibility data in the clinical unit and medical center; severity of illness; relevant comorbidities (eg, neutropenia, recent abdominal surgery); evidence of involvement of the central nervous system, cardiac valves, eyes, and/or visceral organs; and history of intolerance to an antifungal agent.
About 36% of patients refractory to other therapies responded well to caspofungin therapy, while even 70% of patients intolerant to other therapies were classified as responders. Direct comparative studies to other drugs in the treatment of invasive aspergillosis have so far not been undertaken.

The most important side effects been reported are hepatic effects (such as increase of liver enzymes (ALT=SGPT and AST=SGOT)) and sensitivity reactions due to histamine release (rash, facial swelling, pruritus, sensation of warmth and one case of anaphylaxis).

VI.2.3 Unknowns relating to treatment benefits

There is limited data regarding caspofungin use in the following specific populations:

- Neonates and infants <3 months of age. There is limited data available on the safety and effectiveness of caspofungin therapy in these populations
- Pregnancy. There is limited data available of caspofungin therapy during pregnancy

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm *(Hypersensitivity reactions (including histamine-mediated adverse events))*	Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It typically causes a number of symptoms including rash, itching, feeling warm, swelling of the face, lips or throat or difficulty breathing. Stevens-Johnson Syndrome a form of toxic epidermal necrolysis is a life-threatening skin condition, in which cell death causes the outer layer of the skin (epidermis) to separate from the inner layer of the skin (dermis). It usually begins with fever, sore throat, and fatigue. Ulcers and other lesions begin to appear in the mucous membranes, almost always in the mouth and lips,	Treatment should be discontinued

	but also in the genital and anal regions.	
Liver toxicity, increased values of some liver tests *(Hepatotoxicity/increase in liverenzymes)*	Treatment with caspofungin may results in increased values of some liver tests such as alanine transaminase (ALT) and aspartate transaminase (AST). This is also the case when caspofungin is co-administered with cyclosporine (used to help prevent organ transplant rejection or to suppress patient immune system)	Close monitoring of liver enzymes should be considered
Resistance of the fungi to the medicine *(Drug resistance)*	Drug resistance occurs when microbes, such as bacteria, viruses, parasites, or fungi acquire the ability to grow in the presence of a chemical (drug) that would normally kill it or limit its growth. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has been observed. However, the frequency of resistance to caspofungin by various clinical isolates of Candida and Aspergillus is rare	If treatment is not efficacious due to resistance of the microorganism to caspofungin, treatment should be re-considered
Interaction between caspofungin and drugs that initiates or enhances the expression of an enzyme. *(Drug-drug interaction: Rifampicin and other inducers of drug clearance)*	Co-administration of caspofungin with some drugs influence the concentration of caspofungin and therefore it efficacy. On the first day of co-administration the concentration of caspofungin increase however, it levels gradually decreased upon repeated administration.	Caution should be made with co-administration of caspofungin with these drugs. Physician should be informed about other treatments followed by the patient

	These drugs are: • some HIV medicines such as efavirenz or nevirapine; • phenytoin or carbamazepine (used for the treatment of seizures); • dexamethasone (a steroid); • rifampicin (an antibiotic) When co-administering with these kind of drugs, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered in adult patients	
Interaction between caspofungin and cyclosporine A *(Drug-drug interaction: Cyclosporine A)*	Cyclosporine is a drug used to help prevent organ transplant rejection or to suppress the immune system. When caspofungin is co-administered with cyclosporine A, the level of liver tests such as alanine transaminase (ALT) and aspartate transaminase (AST) increases	Close monitoring of liver enzymes should be considered if the two medicinal products are used concomitantly.
Interaction between caspofungin and tarcolimus *(Drug-drug interaction: Tarcolimus)*	Tacrolimus is a drug used to help prevent organ transplant rejection or to suppress the immune system. When caspofungin is co-administered with tarcolimus, the concentration of tacrolimus decreases	For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are mandatory.

Important potential risks	
Risk	**What is known (Including reason why it is considered a p**

	otential risk)
None	

Missing information	
Risk	**What is known**
Additional data on the safety and effectiveness in neonates and infants <3 months of age	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/m2 daily in neonates and infants (less than 3 months of age) and 50 mg/m2 daily in young children (3 to 11 months of age) can be considered. 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/m2 daily dose indicated an AUC0-24 hr within the same range as that observed in older children and adults at the 50 mg/m2 and the 50 mg dose, respectively, while in one 6-month old child receiving the 50 mg/m2 dose, the AUC0-24 hr was somewhat higher. In neonates and infants (<3 months) receiving caspofungin at 25 mg/m2 daily (corresponding mean daily dose of 2.1 mg/kg), caspofungin peak concentration (C1 hr) and caspofungin trough concentration (C24 hr) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, C1 hr was comparable and C24 hr modestly elevated (36 %) in these neonates and infants relative to adults. However, variability was seen in both C1 hr (Day 4 geometric mean 11.73 µg/ml, range 2.63 to 22.05 µg/ml) and C24 hr (Day 4 geometric mean 3.55 µg/ml, range 0.13 to 7.17 µg/ml). AUC0-24 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.
Exposure during pregnancy	*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.

	Caspofungin has been shown to cross the placental barrier in animal studies.

VI.2.5 Summary of risk minimisation 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 minimising 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 minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorization development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	27.03.2015	**Important identified risks** • Anaphylaxis/possible histamine-mediated adverse events • Elevated liver levels • Respiratory adverse events • Phlebitis • Local injection-site adverse events • Pyrexia, rash and headache in paediatric patients **Important potential risks** • Hepatic dysfunction • Compatibility with other intravenous substances, additives or medicinal products **Missing information** • Use in neonates and infants below 12 months of age	Initial version

		• Pregnant and lactating women • Fertility • Long term treatment (longer than 4 weeks) • Use in patients older than 65 years • Ability to drive and use machines	
1.0	21.06.2016	**Important identified risks** • Hypersensitivity reactions (including histamine-mediated adverse events) • Hepatotoxicity/Increase in liver enzymesDrug resistance • Drug-drug interaction: Rifampicin and other inducers of drug clearance • Drug-drug interaction: Cyclosporine A • Drug-drug interaction: Tarcolimus **Important potential risks** • None **Missing information** • Additional data on the safety and effectiveness in neonates and infants <3 months of age • Exposure during pregnancy	Implementation of day 70 and day 100 assessors comments
1.0	20.10.2016	**Important identified risks** • Hypersensitivity reactions (including histamine-mediated adverse events)	SmPC harmonization as per originator's product information and alignment of RMP

		• Hepatotoxicity/Increase in liver enzymesDrug resistance • Drug-drug interaction: Rifampicin and other inducers of drug clearance • Drug-drug interaction: Cyclosporine A • Drug-drug interaction: Tarcolimus **Important potential risks** • None **Missing information** • Additional data on the safety and effectiveness in neonates and infants <3 months of age • Exposure during pregnancy	