VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Overview of disease epidemiology

Invasive fungal infections are increasingly recognized and represent a primary cause of morbidity and mortality in critically ill patients. A variety of factors influence the incidence (a measure of the probability of occurrence of a given medical condition in a population within a specified period of time) and severity of invasive fungal infections.

The yearly incidence of invasive candidiasis (serious fungal infections in tissues or organs caused by fungal (yeast) cells called Candida) was reported as 7.28/100 000 population. Lower rates were determined in Finland and Sweden. Invasive candidiasis incidence is much higher among infants than in adults and children from other age groups. The incidence of invasive aspergillosis (fungal infections in nose, nasal sinuses or lungs caused by a mould called Aspergillus) varies according to underlying diseases, pathogen and geographic location; rates of up to 7% are reported in Europe. Resistant strains of Aspergillus have currently been reported. The potential frequency of cross resistance amongst echinocandins (an antifungal drug) in Aspergillus species is still unclear. The epidemiological data and clinical finding for invasive aspergillosis in non neutropenic patients are not identical to those in neutropenic patients.

VI.2.2 Summary of treatment benefits

In accordance with available data of clinical trials caspofungin has similar efficacy to azoles and is at least as effective as amphotericin B. Thus, caspofungin provides an alternative to triazoles or amphotericin B in oesophageal candidiasis, (a localized fungal infection of the foodpipe), invasive candidiasis and invasive aspergillosis.

- **Invasive Candidiasis in Adult Patients:**

  An initial study including two hundred thirty-nine patients to compare caspofungin and amphotericin B for the treatment of invasive candidiasis showed a favourable response required both symptom resolution and microbiological clearance of the Candida infection.

  In a second study, 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 treatments groups, respectively.

- **Invasive Aspergillosis in Adult Patients:**

  In an open-label study including sixty-nine adult patients with invasive aspergillosis 41% (26/63) of patients receiving at least one dose of caspofungin had a favourable response (required clinically significant improvement in radiographs as well as in signs and symptoms). 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.

- **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. There were 1,095 patients included in the primary Modified Intention To Treat (MITT) efficacy analysis of overall favourable response (required meeting each of 5 criteria: Successful treatment of any baseline fungal infection; no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment; no discontinuation from the study drug because of drug-related toxicity or lack of efficacy; resolution of fever during the period of neutropaenia) caspofungin (33.9 %) was as effective as liposomal amphotericin B (33.7 %).

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).

- **Paediatric Population:**

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

  The first study, which enrolled 82 patients between 2 to 17 years of age, was a randomized, double-blind study comparing caspofungin to liposomal amphotericin B as empirical therapy in paediatric patients with persistent fever and neutropenia. The overall success rates in the Modified Intention To Treat (MITT) analysis results were 46.6 % (26/56) for caspofungin and 32.3 % (8/25) for liposomal amphotericin B.

  The second study was a prospective, open-label, non-comparative study estimating the safety and efficacy of caspofungin, which enrolled forty-nine patients with invasive Candidiasis, esophageal candidiasis and invasive aspergillosis (ages 6 months to 17 years). The favourable response rate, by indication, at the end of caspofungin therapy was in the MITT analyses 81% (30/37) in invasive candidiasis, 50% (5/10) in invasive aspergillosis and 100% (1/1) in esophageal candidiasis.

VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

The safety and efficacy in pregnant and breast feeding women has not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hepatotoxicity	Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and paediatric patients treated with caspofungin.	Yes, by monitoring the evidence of worsening hepatic function. A reduction of the daily dose to 35 mg is recommended for adults with

Risk	What is known	Preventability
	In adult patients with mild and moderate hepatic impairment, the AUC (the area under the curve represents the total drug exposure over time) is increased about 20% and 75%, respectively. There is no clinical experience in adults with severe hepatic impairment or in paediatric patients with any degree of hepatic impairment.	moderate hepatic impairment. Caspofungin should be used with caution in patients with severe hepatic impairment.
Hypersensitivity reactions (including histamine-mediated allergic reactions)	There have been reports of histamine mediated adverse reaction, such as rash, facial swelling, angioedema, pruritus, sensation of warmth or bronchospasm.	Yes, by monitoring for early symptoms. The rapid infusion should be avoided. Caspofungin is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. Routine Risk minimisation measures are in force. The comprehensive and well readable PIL is effective to prevent the risk.
Drug resistance	Candida with reduced susceptibility to caspofungin has been identified in a small number of patients. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has been observed. The incidence of resistance to caspofungin by various clinical isolates of Candida and Aspergillus is rare.	Routine Risk minimisation measures are in force. The comprehensive and well readable PIL is effective to prevent the risk.
Drug-drug interaction: Rifampin and other inducers of drug clearance	Rifampin (an antibiotic) caused an increase in trough concentration (the lowest concentration at which a	Routine Risk minimisation measures are in force. The comprehensive and well readable PIL is effective to

Risk	What is known	Preventability
	medication is present in the body) of caspofungin on the first day of co administration when both medicinal products were initiated together in healthy adult volunteers. 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.	prevent the risk.
Drug-drug interaction: Cyclosporine A	Some healthy adult volunteers who received two 3 mg/kg doses of cyclosporine (used to help prevent organ transplant rejection or to suppress your immune system) with caspofungin showed transient increases in liver enzymes, such as 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 caspofungin and cyclosporine no serious hepatic adverse reactions were noted. Furthermore, in two clinical studies performed in healthy adult subjects, cyclosporine A increased the AUC of caspofungin by approximately 35 %. These AUC increases are probably due to reduced uptake of caspofungin by the liver.	Close monitoring of liver enzymes should be considered if caspofungin and cyclosporine are used concomitantly. Routine Risk minimisation measures are in force. The comprehensive and well readable PIL is effective to prevent the risk.

Risk	What is known	Preventability
Drug-drug interaction: Tacrolimus	Caspofungin reduced the trough concentration of tacrolimus (substance to prevent organ transplant rejection or to suppress the immune system) by 26% in healthy adult volunteers.	For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are mandatory. Routine Risk minimisation measures are in force. The comprehensive and well readable PIL is effective to prevent the risk.

Important potential risks

None.

Missing information

Risk	What is known
Exposure during pregnancy	For use in pregnancy, no or limited data are available. The potential risk is therefore unknown. Caspofungin should not be used during pregnancy unless clearly necessary.
Additional data on the safety and effectiveness in neonates and infants <3 month	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.

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.

The Summary of Product Characteristics and the Package leaflet for Caspofungin can be found on the webpages of the National Competent Authorities..

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	Initial submission of MAA.	-	-
2.0	09.03.2016	Adaption to reference product and RMP template for generics.	Update of – Identified Risks – Potential Risks – Missing information – Format of RMP – Part VI
3.0	15.06.2015	-	Update according to additional comments in the DCP
3.1	11.07.2016	-	Minor Corrections
3.2	04.08.2016		Minor Corrections Part I