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Product name: **CANCIDAS**
Procedure No. **EMEA/H/C/379/II/02**

SCIENTIFIC DISCUSSION

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1 Introduction

Caspofungin acetate is a semi-synthetic lipopeptide compound of the echinocandin family and represents a new class of antifungal agents (glucan synthesis inhibitors) that inhibits the synthesis of beta (1,3)-D-glucan an integral component of the fungal cell wall. Caspofungin MSD was granted a Marketing Authorisation under exceptional circumstances on 24 October 2001, indicated in the treatment of invasive aspergillosis in adults, who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. The approved dosage is a single 70-mg loading dose on day 1, followed by 50 mg thereafter. Duration of treatment is not specified and is to be based upon the severity of the patient's underlying disease, recovery from immmunosuppression and clinical response. The Marketing Authorisation Holder (MAH) has committed to specific obligations and follow-up measures. Pursuant to article 13 (2) of Council Regulation (EEC) No 2309/93 and part 4 G of the Annex I to Directive 2001/83/EC, the MAH has agreed to provide, as requested by the CPMP, additional clinical data. These data will form the basis for a re-assessment of the benefit/risk ratio of Caspofungin MSD in the treatment of invasive aspergillosis.
Caspofungin has also been given a Marketing Authorisation in the indication salvage treatment of invasive aspergillosis in the United States on 29 January 2001 and in 20 further countries including Canada, Australia and Brazil. In addition, caspofungin has recently been approved for the primary treatment of eosophageal candidiasis (EC), and in some instances oropharyngeal candidiasis (OPC) in 5 countries in South Americe and the United States.

The application initially submitted by the MAH concerned a Type II variation (EMEA/H/C/379/II/02) to extend the indication to the treatment of "*Invasive candidiasis (IC), including candidaemia in neutropenic and non-neutropenic patients*". The recommended dose regimen was a single loading 70-mg loading dose followed by 50 mg daily thereafter, administered by slow intravenous infusion over approximately 1 hour. The duration of treatment was to be based upon the patient's clinical and microbiological response, but in general therapy should be continued for at least 14 days after the last positive culture.

2 Toxico-pharmacological aspects

For this type II variation, no additional part IIIdata has been submitted by the MAH. The MAH referred to some new preclinical evaluations, however, the references included were already available for the prior applications. There were some new studies with caspofungin published in the scientific literature. The pharmacological/toxicological aspects of caspofungin have been discussed in previous reports concerning use in invasive aspergillosis, as well as oropharyngeal and oesophageal candidiasis. The usefulness of caspofungin in disseminated candidiasis was previously studied in various animal survival models and in target organ assays and overall good activity was demonstrated. In most of these studies animals were infected with strains of *C. albicans*, but some data on target organ kidney assays from studies using other strains of *Candida* were also available. Published data in knockout mice suggested also efficacy of caspofungin *in vivo* using strains of *C. glabrata*.

Concerning the toxicity of caspofungin, the CPMP concluded that the proposed posology for the present indication did not suggest that a reconsideration of these aspects be warranted. From a preclinical point of view, no new issue have been identified. Therefore, the CPMP considered that there was no preclinical objection for an extension of the indication of caspofungin to include IC.

3 Clinical aspects

3.1 Clinical pharmacology

- **Pharmacodynamics**

The population pharmacokinetics analysis for Protocol 014 explored the potential for $C_{1\ hr}$, $C_{24\ hr}$, $C_{1\ hr}$/MIC and $C_{24\ hr}$/MIC to predict overall (clinical and microbiologic response) treatment outcome (favorable/unfavorable). Subpopulations of patients with similar infection characteristics were also explored in a series of secondary analyses. However, the CPMP considered that none of the parameters examined was found to be a significant factor for predicting the overall treatment outcome.

- **Pharmacokinetics**

The basic pharmacokinetic characteristics of caspofungin have been well defined in previous applications concerning invasive candidiasis. The present file completed this information with the results of:

1. A repeated study of long-term disposition of radioactive caspofungin, extended to 6 months follow-up. These data confirmed that no parental drug was present in significant concentration after a mean of 6 days postdose, and no further metabolites were identified. Such data were required as a follow-up measure in the initial IA dossier. Therefore, they will be further analysed in the assessment of this commitment.
2. A Phase I pharmacokinetic study of single doses of caspofungin up to 210 mg, as well as daily doses of 100 mg, suggesting little accumulation. These data were not directly related to the current dossier.
3. A small study supporting the dose adaptation proposed in the SPC for patients with mild to moderate hepatic insufficiency (i.e., no adjustment for mild insufficiency and a decrease in the daily dose from 50 to 35 mg for moderate insufficiency). No patients with severe hepatic insufficiency were analysed.
4. Drug interaction pharmacokinetic studies with rifampin and nelfinavir.

   In patients already treated with rifampin, an increase in the daily dose of caspofungin, for instance to 70 mg instead of 50 mg, could be considered to achieve the same target plasma concentrations. However, if rifampin was started during caspofungin treatment, no dose adjustment appeared necessary. Nelfinavir did not interact with caspofungin pharmacokinetics.

   The drug interaction screen performed as part of the population pharmacokinetic analysis in IC patients did not bring any new information. The CPMP concluded that the current recommendation to increase the dose of caspofungin with concomitant inducer drugs should be kept.

5. A population pharmacokinetic analysis in the pilot study P014.

   As in the previous IA file, the population pharmacokinetics of caspofungin in IC patients was based exclusively on time-averaged parameters (mean $C_{1\ hr}$ and $C_{24\ hr}$ from Day 3 to Day 14). This procedure smoothed out some of the high variability in individual plasma concentrations, but it may have clouded the analysis of PK/PD relationship.

   Time-averaged $C_{1\ hr}$ and $C_{24\ hr}$ were somewhat lower in IC patients than in the previous IA and EC/OPC groups. The MAH suggested that the parallel decreases in $C_{1\ hr}$ and $C_{24\ hr}$ in IC patients compared with IA and EC/OPC patients and healthy subjects were due to an increase in the apparent volume of distribution. Alteration in caspofungin plasma protein binding in severely ill patients, such as IC patients in Protocol 014, was a possible explanation, although it did not fit well with the higher plasma concentrations observed in IA patients, who were similarly ill. On the

other hand, the septic nature of the infections in IC patients, which was more conspicuous than in IA patients, may have generated a greater inflammatory response and associated increase in vasopermeability and/or an enhanced binding of caspofungin to fungal organisms within the blood than in other patients. Both of these potential mechanisms could have lead to reduced caspofungin plasma concentrations in IC patients relative to other patients or healthy subjects.
The CPMP nevertheless felt that in view of the recent determinations of the free fraction of caspofungin in the plasma, the SPC (Section 5.2) should be adapted to include the full range of free fractions of caspofungin measured. The different evaluations of the fraction unbound may be relevant in some clinical situations.
Finally, the CPMP agreed on the fact that the reductions in caspofungin concentrations in IC patients relative to other groups of patients/subjects did not appear to be clinically meaningful, given the high proportion of favourable responses obtained with caspofungin treatment and the lack of statistically significant correlations between treatment outcome and caspofungin concentrations in IC patients.

Special populations:

Elderly (≥ 65 years) patients have a ~40 % increase in plasma trough (but not peak) concentrations of caspofungin. As a consequence, no dose adjustment was required.

Heavier weight patients have decreased end-of-infusion and trough concentrations. Although this decrease was somewhat less than observed for IA and EC/OPC patients, possibly because caspofungin plasma concentrations were lower in IC patients than the other two categories, an increase in daily dose from 50 to 70 mg was nevertheless recommended by the CPMP in patients weighing more than 80 kg, exactly as stated for the other categories of patients, for the benefit of optimal exposure. Section 5.2 of the SPC has therefore been amended to include a dose adjustment to 70 mg in invasive candidiasis patients weighing >80 kg.

Dose finding:

The selection of the caspofungin dose of 70 mg I.V. on Day 1 followed by 50 mg I.V. daily for the treatment of IC was exactly the same as for the treatment of IA. It was based on a target $C_{24\ hr}$ of >1 µg/ml, and on data from 2 dose-ranging Phase II studies involving EC and OPC patients (Protocols 003 and 004), a range of 3 doses (35, 50, and 70 mg), and a comparison with amphotericin B. However, due to the high proportion of favourable responses in these EC/OPC patients, both with caspofungin and amphotericin B, this particular dose-finding process was not very sensitive. The MAH explained that the dose-finding studies were not performed in invasive candidiasis because of the severity of this disease. However, the dose selection based on Phase I-II studies in patients with oesophageal candidiasis may not have been optimal, since this is after all a mucosal disease which differed in several ways from a more invasive setting of *Candida* infection. Nevertheless, two elements justified the use of a caspofungin dose of 50 mg IV daily after a 70-mg loading dose on Day 1 in IC patients:
- the confirmation of a high treatment response in all IC patients;
- the fact that in the population pharmacokinetic study, no parameter ($C_{1\ hr}$, $C_{24\ hr}$, AUC, $C_{1\ hr}$:MIC, $C_{24\ hr}$:MIC) was found to significantly predict treatment outcome (not even in any clinically relevant subpopulation).

- **Pharmacokinetic/pharmacodynamic relationship**

The pharmacokinetic/pharmacodynamic relationship of caspofungin in IC was assessed in Protocol P014. This was an important issue, since no particular plasma trough or peak concentration of caspofungin had been established as the absolute minimum concentration for efficacy. In Protocol P014, neither end-of-infusion nor trough concentrations predicted overall treatment outcome in evaluable IC patients (this group of patients has an 80 % proportion of favorable outcomes with caspofungin therapy). The MAH concluded that the range of concentrations obtained in Protocol 014 fall near the top of the concentration-response curve, where treatment response had, at most, only a modest concentration-dependency. The CPMP acknowledged that even when using more sensitive

measures of outcome, such as time to negative culture, and/or when restricting the analysis to the MITT population, the plasma levels of caspofungin after daily 50-mg administrations, whether trough ($C_{24\ hr}$) or peak ($C_{1\ hr}$) concentrations, did not appear to predict the treatment outcome of invasive candidiasis (IC) in any significant way. Thus, the MAH's suggestion was accepted.

In addition, the occurrence of adverse experiences in IC patients was not increased by higher caspofungin plasma concentrations over the wide range of pharmacokinetic parameter values observed in Protocol 014.

- **Microbiology**

Overall 226 unique baseline isolates were collected from 211 of the 239 patients enrolled in the pivotal study. Only 45% of the 211 patients had an infection with *C. albicans*. The 3 most commonly noted non-*albicans* pathogens were *C. parapsilosis* (19.0%), *C. tropicalis* (16.1%) and *C. glabrata* (11.4%). The remainder of the patients (8.5%) had infections with rarer *Candida* species or mixed infections. Outcomes by *Candida* species and MIC were performed to define spectrum of activity for caspofungin against the various *Candida* pathogens, the range of susceptibility patterns and MIC values predictive of outcome. The caspofungin MICs for *C. albicans* ranged from 0.125 to >8 μg/ml, with a MIC_{90} of 1 μg/ml. For *C. glabrata*, the MICs ranged between 0.25 and 2 μg/ml, with a MIC_{90} of 2 μg/ml. The caspofungin MICs for *C. parapsilosis*, *C. tropicalis*, and *C. krusei* ranged from 0.5 to >8 μg/ml, but the MIC_{50} and/or MIC_{90} were generally ≤2 μg/ml. The favourable overall response rates in both treatment groups were similar and did not appear to vary either by *Candida* species or by MIC values, although there was a slightly lower response rate for infections caused by *C. albicans* as compared to those caused by non-albicans species. There was thus no apparent correlation between the baseline MIC values for caspofungin and the overall clinical and microbiological outcomes, and therefore break-point MIC determinations for the treatment of IC could not be established. No evidence of resistance development against caspofungin was observed.

- **Conclusion**

The CPMP agreed on the dose of caspofungin in the treatment of invasive candidiasis which has been set at 50 mg daily (except in patients weighing >80 kg, where it should be 70 mg daily) after a loading dose of 70 mg. In the population pharmacokinetic study, no parameter ($C_{1\ hr}$, $C_{24\ hr}$, AUC, $C_{1\ hr}$:MIC, $C_{24\ hr}$:MIC) was found to significantly predict treatment outcome. The free fraction of caspofungin varied markedly between studies and this point has been mentioned in the SPC.

3.2 Clinical efficacy

The MAH presented efficacy data from a phase III invasive candidiasis study (Protocol 014) including a total of 239 patients. This study was a multicenter, randomised, double blind (and in-house blind) study comparing the efficacy, safety, and tolerability of caspofungin to amphotericin B (AmB) performed during Nov 1997 to July 2001. The study was powered to demonstrate the non-inferiority of caspofungin to AmB with regards to efficacy in all patients with IC and in the subset of patients with candidemia. The study was also powered to assess the potential superiority of caspofungin versus AmB for a number of safety variables.

The MAH also presented data from 11 patients with IC who were refractory to or intolerant of an IV AmB formulation (either as conventional amphotericin or a lipid formulation) enrolled in the compassionate use study (Protocol 024/025). The purpose of the interim report was to lend further support to the use of caspofungin in invasive *Candida* infections, also in cases where available antifungal regimens, including IV AmB formulations, have failed. Patients enrolled in this study represented a difficult-to-treat population.

Table: Clinical studies supporting caspofungin efficacy in invasive candidiasis

Protocol/ [Ref.]/ (Short Title)	Phase	Major Entry Criteria	Treatment Daily Doses (mg)/Duration (N†)	Primary Efficacy Endpoints
Efficacy in Candidiasis				
014 [P014] (Phase III Invasive Candidiasis Study)	III	Clinically and microbiologically documented cases of invasive candidiasis	Caspofungin doses of 50 daily (following a 70-mg loading dose on Day 1) versus amphotericin B 0.6 to 1.0 mg/kg daily for variable duration (at least 10 days and maximum of 28 days) (N=239)	Overall response (clinical response and micro-biological response)
024/025 [P024C3] (Compassionate Use Study)	NA	Definite or probable *Aspergillus* infections; documented invasive candidiasis, oropharyngeal candidiasis, or *Candida* esophagitis in patients refractory to or intolerant of an amphotericin B formulation	For invasive *Candida* infections, caspofungin 50 mg daily (following a 70-mg loading dose on Day 1) for variable duration (N=11)	Resolution or clinically meaningful improvement in attributable symptoms
† N=Number of patients enrolled in each study.				

Entry criteria: Adults ≥18 years of age with both microbiological and clinical evidence of invasive *Candida* infection were eligible. The microbiological criteria required at least 1 positive culture of a *Candida* species from blood or from another normally sterile body site obtained within 4 days of study entry. Clinical evidence of infection included either presence of fever, hypothermia, hypotension or other signs of inflammation from a site infected with *Candida* within 48 hours. Patients with infections that had prior failed antifungal therapy and patients who received greater than >2 days of prior antifungal therapy for this episode of IC were excluded. Eye exams were performed on all patients prestudy and at predefined visits to assess the presence of *Candida* endophthalmitis. In patients with candidemia blood cultures were collected twice daily until negative (at 48 hours). Patients were stratified by the presence of neutropenia (ANC ≤500 or >500 µl) and by APACHE II score (≤20 or >20) and then randomised to receive either caspofungin (70 mg for 1 day followed by 50 mg/day) or amphotericin B (0.6 to 0.7 mg/kg/day for non-neutropenic patients and 0.7 to 1.0 mg/kg/day for neutropenic patients). Patients were to be treated for 14 days after the last positive culture. IV study therapy was continued until clinical improvement and for ≥48 hours after the last positive culture. The min and max duration of IV therapy was 10 and 28 days, respectively. On Day 10 of therapy, the patients were evaluated and could be switched to oral fluconazole at 400 mg/day to complete the treatment course. Patients with infections caused by *C. krusei* or *C. glabrata* were to remain on IV study therapy.

Efficacy endpoints: To be considered a favourable response the patients had to have both a favourable clinical response and a favourable microbiological response, this composite endpoint is referred to as the overall response. The primary efficacy endpoint was the proportion of caspofungin patients with a favourable overall response at the time of discontinuing IV therapy compared with that of AmB patients. Secondary efficacy endpoints included assessment of the overall response at Day 10, end of IV therapy, end of all antifungal therapy and at two post-therapy follow-up visits (2 week and 6-8 week). Mortality by study therapy was also analysed. The individual components of the composite endpoint, clinical or microbiological response, were also displayed for the end of IV therapy visit. A favourable clinical response was defined as resolution of all signs and symptoms related to the *Candida* infection. Clinical failure was defined as persistence of signs and symptoms of infection. A favourable microbiological response, eradication or presumed eradication, was defined as having negative cultures from the original site of infection or no follow-up cultures in the setting of clinical and radiographic resolution.

Safety endpoints: Predefined safety endpoints included comparison of the proportion of patients in the caspofungin group versus those in the amphotericin B group who experienced nephrotoxicity, hypokalemia, an infusion-related-related AE, a drug-related AE, or who discontinued therapy due to an drug-related AE. The nephrotoxicity assessment was the primary safety analysis.

Statistical planning: A modified intention-to-treat (MITT) was the primary analysis and included patients who met the definition of disease and received at least 1 dose of therapy (n=224). The supportive analysis included Evaluable Patients (EP) defined as patients who met the definition of disease, received at least 5 full days of therapy and did not commit any major protocol violations (n=185). The overall efficacy response in the 2 treatment groups was compared at the end of IV study therapy using a noninferiority analysis. The definition of noninferiority stated that (1) the two-sided 95.6% CI for the difference between the 2 treatment groups for the favourable overall response (defined as the strata-adjusted caspofungin response minus the strata-adjusted AmB response) would include zero, and (2) the lower limit of the CI would not exceed -20.0%. Superiority of caspofungin over AmB would be concluded if the lower limit of the two-sided 95.6% CI for the difference in responses was above 0. As a predefined secondary analysis, a separate noninferiority analysis was performed on the subset of patients with candidemia at the end of IV therapy visit. In this subset, Kaplan Meier estimates were also displayed for time to negative blood culture.

Demographics: Altogether 239 (114 on caspofungin and 125 on AmB) received IV study therapy. The majority of the patients enrolled were men (55.6%). The treatment groups were comparable with respect to gender, racial origin, and age. A similar proportion of patients in both treatment groups (20%) were found to have high APACHE II scores (>20) in the pre-study period. A similar proportion of patients in both treatment groups, was noted to be neutropenic (total n=26) at baseline. Overall 184 (77%) patients had candidemia alone, with the percentages in each group being comparable. Approximately 8% (n=19) of the patients had *Candida* peritonitis. The mean duration of study therapy was 11.8 days for caspofungin and 11.3 days for AmB.

- **Dose-response studies and main clinical studies**

The selection of the caspofungin dose of 70 mg on day 1 followed by 50 mg daily for the treatment of IC was based on an integration of previous data from the in vitro and in vivo preclinical studies, human PK analyses and the safety and efficacy results from two dose-ranging phase II EC and OPC studies (P003, P004). The loading dose of caspofungin 70-mg was used since it has been shown to provide higher trough levels in the early critical stage of treatment and also to provide a more rapid achievement of steady state than the corresponding regimen without loading.

- **Clinical studies in special populations**

The study population in the invasive candidiasis study consisted of a heterogeneous patient population, all with critical illnesses but different risk factors for an invasive *Candida* infection. No other special populations were targeted.

- **Supportive studies**

The Compassionate use study (Protocol 024/025) was an ongoing study enrolling patients with IC (along with EC, OPC, or IA) who were refractory to or intolerant of an IV amphotericin formulation. Refractory disease was defined as clinical or microbiological progression of disease or lack of improvement despite therapy for 7 days with either amphotericin B or a lipid amphotericin formulation. Intolerance was defined as developing renal insufficiency (creatinine ≥2.5 mg/dl) or acute severe infusion-related toxicity while on amphotericin. The dosage regimen was the same as that in the IC study whereas duration of therapy was individualised based on the underlying disease and clinical response. The primary efficacy assessment was made at the end of IV therapy.

The results from 11 patients were analysed. The sites of invasive infection varied: 3 patients had chronic disseminated candidiasis (or hepatosplenic candidiasis), 1 patient had candidemia, and 1 had *Candida* peritonitis. Three patients had infections of the urinary system, including one patient each with a kidney abscess, recurrent pyelonephritis, and a complicated bladder infection. Three patients manifested multiple sites of infection.

Nine of the patients were refractory to an amphotericin formulation. Eight of the 9 patients clinically refractory to an AmB formulation had received multiple antifungal agents (including azoles and 5-FC) either sequentially or concomitantly prior to entry into the study. All 8 patients had also failed prior

therapy with an azole. Two patients were only intolerant to prior therapy with an AmB formulation. A favourable clinical response at the end of caspofungin therapy was seen in 8 (80.0%) of the 10 evaluable patients. This included 4 patients who had a complete response and 4 patients with a partial response. The duration of caspofungin therapy was prolonged in these patients with a mean duration of 32.3 days.

- **Discussion and conclusions on efficacy**

To extend the indication to treatment of invasive candidiasis, the applicant submitted 1 new pivotal phase III study, Protocol 014.

The proportion of patients in the MITT analysis, the primary analysis, and in the EP analysis with a favorable response, adjusted for strata, at the discontinuation of IV study therapy, the primary endpoint, (except for the follow-up data), and the respective 95% CI for each analysis and observed difference, are summarized in the table below.

Table: Proportion of patients with a favourable response and the difference between treatment groups

Visit	**Caspofungin 70 mg/50 mg**			**Amphotericin B 0.6-1 mg/kg**			**Observed difference**	
End of IV study therapy	N/m	(%)	(95%CI)	N/m	(%)	(95%CI)	(%)	(95%CI)
Overall combined response								
MITT	**80/109**	**74.2**	**(66.0, 82.3)**	**71/115**	**61.5**	**(52.6, 70.4)**	**12.7**	**(-0.7, 26.0)**
Evaluable patients	71/88	80.2	(72.3, 89.2)	63/97	65.3	(55.7, 74.9)	15.4	(1.1, 29.7)
Clinical response								
MITT	82/109	75.2	(67.1, 83.4)	71/115	61.7	(52.8, 70.7)	13.5	(1.5, 25.5)
Microbiological response								
MITT	92/109	84.4	(77.6, 91.2)	91/115	79:1	(71.7, 86.6)	5.3	(-4.8, 15.4)
Overall response and relapse at 6-8 week follow-up								
MITT response	47/83	56.6	(45.9, 67.4)	47/99	47.5	(37.6, 57.4)	9.2	(-5.4, 23.7)
Relapse	7/80	8.8	(2.5, 15.0)	8/71	11.3	(3.9, 18.7)	-2.5	(-12.1, 7,1)
Overall response by neutropenic stratum								
Neutropenic	7/14	50.0	(22.8, 77.2)	4/10	40.0	(8.0, 72.0)	10	(-30.0, 50.1)
Non-neutropenic	73/95	76.8	(68.3, 85.4)	67/2 105	63.8	(54.6, 73.0)	13.0	(0.5, 25.5)
Overall response in candidemia								
MITT	66/92	72.5	(63.8, 81.5)	59/94	62.5	(52.7, 72.3)	10.0	(-4.5, 24.5)

The CPMP concluded that the results of the MITT and EP analyses and of other efficacy variables were consistent, with always a numerically higher success rate in the caspofungin group than in the amphotericin B group. Nevertheless, a more rational delta value should have been selected for this indication. Delta was set at 20% and should have been smaller as specified in the CPMP Note for Guidance on anti-infective agents.
One of the main reasons for the difference in overall response between both treatment groups was due to a significant difference in the development of drug-related adverse experiences, with significant more toxicity in the amphotericin B group. The definition of failure was thus apparently not entirely based on efficacy variables but also included a safety variable, which had a negative impact on the amphotericin B outcome. In addition, the dosage of amphotericin B given in the non-neutropenic patients was 0.6 to 0.7 mg/kg/day, which was rather low and might mean that certain patients in the amphotericin B treatment arm could have been underdosed. However, it was the CPMP's opinion that all temporary interruptions in therapy were adequately explained and did not probably influence outcome. With regard to amphotericin B underdosing, the CPMP accepted that only few patients (8) were truly underdosed (< 0.55 mg/kg/day), and that among these 4 responded favourably and 3 had amphotericin B-related toxicity, considering that the MAH has accepted to restrict the indication to non-neutropenic patients. Thus, the consequences of inadequate amphotericin B should not have biased the results in favour of caspofungin.

Patients were stratified by the presence of neutropenia and APACHE II score. The number of neutropenic patients enrolled in this study was considered too limited to draw conclusions on the effectiveness of caspofungin in neutropenic patients (only 14 neutropenic patients received caspofungin). Therefore, the CPMP concluded that the indication initially proposed by the MAH

should be restricted to "*Invasive Candidiasis in non-neutropenic patients*". Furthermore, the MAH commited to obtain more data on caspofungin in the treatment of neutropenic patients by providing results from an ongoing prospective, randomised, double-blind study assessing the use of caspofungin versus liposomal amphotericin B (AmBisome™) for the empirical treatment of patients with persistent fever and neutropenia despite antibiotic therapy (Protocol 026).

A separate non-inferiority analysis was also performed in a subset of patients with candidaemia, which consisted of 80% of the overall invasive candidiasis population. Results were very similar to the results in the overall invasive candidiasis population.

Efficacy data in patients with non-blood sites of infection were very limited (20% of the overall invasive candidiasis population with an overall number of 43 patients) and although results in these patients seemed quite promising, they were too limited to draw robust conclusions. Therefore, the CPMP requested the MAH to commit to collect and present more data in patients with non-blood sites of Candida infections.

Patients with *Candida* endocarditis, osteomyelitis, or meningitis were excluded from this study, since these infections often need prolonged treatment, sometimes combined with surgical interventions. As a result, there were no data on long-term treatment with caspofungin for these types of invasive *Candida* infections. Follow-up data for all enrolled patients were only available for up to 6- to 8-weeks post-therapy, which is rather limited since late relapses could occur after this time period. Therefore, the CPMP requested the MAH that, due to the relapsing/recurring nature of invasive candidiasis, to continue collecting data on more patients at 3 months or more post-therapy.

Finally, patients were frequently switched to oral fluconazole to finish their treatment. This is adequately addressed in the SPC.

3.3 Clinical safety

- **Patient exposure**

In the prior applications for invasive aspergillosis and localized candidiasis (EC and OPC), safety data of 631 patients and subjects treated with caspofungin were submitted, supplemented with the serious adverse experiences collected in the Merck Worldwide Adverse Experience System (WAES) database in another 280 patients treated with caspofungin in ongoing clinical pharmacology and clinical studies.

In this variation, the MAH submitted CRF data from another 245 patients and subjects enrolled in 5 clinical pharmacology studies and 2 clinical studies, enlarging the safety database up to a total of 876 patients. Serious adverse experiences since the cut off date for the localized candidiasis application collected in the WAES database provided further safety data in approximately 300 patients enrolled in 3 ongoing open-label and 1 ongoing blinded study. There were also 53 postmarketing adverse experience reports submitted.

- **Adverse events and serious adverse events/deaths**

Consistent with the initial applications, the most common drug-related clinical adverse experiences in these supplemental studies included fever/chills, phlebitis/infused vein complication, vomiting and headache. Most of them were mild and very few of them led to discontinuation of therapy.

The pivotal invasive candidiasis study allowed for a comparison of the safety of caspofungin to that of amphotericin B. Fewer patients on caspofungin than on amphotericin B developed a drug-related adverse experience and discontinued for any drug-related (clinical or laboratory) adverse experience. Caspofungin was also associated with significantly fewer cases of nephrotoxicity, hypokalemia, and systemic infusion-related adverse events than amphotericin B. This was not completely unexpected when taking into account the toxicity profile of amphotericin B. Toxicity was indeed one of the main reasons for the difference observed in the overall responses between both treatment groups.

Some of the previously identified adverse events associated with caspofungin therapy occurred at somewhat higher frequencies in the IC trial and the SPC has been amended accordingly.
Although no new cases of anaphylaxis were reported in this submission, other histamine-mediated symptoms like rash, flushing, bronchospasm, etc have been identified in a number of cases. Therefore, bronchospasm have been added in the SPC. Although most of these adverse experiences were mild in intensity, vigilance should remain, considering the potential seriousness of hypersensitivity reactions.
No new controlled data were provided on the long-term safety of caspofungin.

- **Laboratory findings**

Decreased serum potassium, increased alkaline phosphatase, increased AST and increased ALT were the most frequently reported drug-related laboratory adverse experiences, which in most cases did not limit therapy.

- **Safety in special populations**

In the pharmacological trial Protocol 036 it was demonstrated that higher doses of caspofungin, 100 mg for 3 weeks, in general was well tolerated in healthy subjects, although the rate of infusion-related AEs was increased.
In Protocol 030, including patients with mild/moderate hepatic insufficiency, no hepatotoxic reactions or other serious AEs occurred in association with administration of caspofungin. There was nevertheless an increased incidence of infusion site related adverse experiences noted in subjects with hepatic insufficiency.

- **Conclusions on safety**

The safety profile of caspofungin remained globally favourable. The occurrence of bronchospasm has been added to the list of existing adverse reactions.

4 Conclusion

The CPMP agreed on the dose of caspofungin in the treatment of invasive candidiasis which has been set at 50 mg daily (except in patients weighing >80 kg, where it should be 70 mg daily) after a loading dose of 70 mg. In the population pharmacokinetic study, no parameter ($C_{1\ hr}$, $C_{24\ hr}$, AUC, $C_{1\ hr}$:MIC, $C_{24\ hr}$:MIC) was found to significantly predict treatment outcome. The free fraction of caspofungin varied markedly between studies and this point has been mentioned in the SPC.

The CPMP concluded that the efficacy of caspofungin in invasive candidiasis was reasonably well demonstrated by comparison with the standard therapy amphotericin B. However, in the clinical studies the number of cases of neutropenic patients was too low to assert the efficacy of caspofungin for invasive candidiasis in such patients. Due to the importance and specificity of this subpopulation, the requested indication has been restricted to "*Invasive Candidiasis in non-neutropenic patients*".

The CPMP concluded that the safety profile of caspofungin remained globally favourable.

Therefore, the CPMP considered that the overall benefit-risk ratio of caspofungin in the treatment of invasive candidiasis (IC) was favourable, and that a marketing authorisation may thus be granted, provided that the MAH commited to the following follow-up measures:

1. Collect more data in neutropenic patients by submitting the study report of protocol 026 to the CPMP by the end of 2003.

2. Collect and present more data in patients with non-blood sites of Candida infections, and propose a timetable to this aim. Due to the relapsing/recurring nature of invasive candidiasis,

to continue collecting data on more patients at 3 months or more post-therapy and present a strategy to this aim.

III. CONCLUSION

The CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics and reflected into the Package Leaflet, based on the observations and the appropriate conclusions.

The CPMP adopted on 21 November 2002 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.