

## SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Cancidas. For information on changes after approval please refer to module 8b.

### 1. Introduction

Caspofungin MSD contains caspofungin which is an antifungal agent indicated in the treatment of invasive aspergillosis in adult 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.

Caspofungin is a semi-synthetic lipopeptide compound of the echinocandin family, synthesised from a fermentation product. It is the first representative of a new class of antifungal agents (glucan synthesis inhibitors) that inhibit the synthesis of beta (1,3)-D-glucan, an integral component of the fungal cell wall. Caspofungin MSD is a sterile, lyophilised product for intravenous infusion that contains 50 or 70 mg caspofungin, corresponding to 55.5 or 77.7 mg caspofungin acetate. The recommended dose is 70 mg as a single loading dose on Day 1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, the recommended dose is 70 mg daily, after the initial 70 mg loading dose on Day 1. The duration of treatment is based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

Due to the increasing number of patients with solid organ and bone marrow transplants, with HIV infections and critical illnesses, which often require invasive procedures, the incidence and the clinical importance of serious fungal infections have risen dramatically in the last 2 decades.

*Aspergillus* is the second most common fungal pathogen after *Candida* and is responsible for up to 30 % of all fungal infections in cancer patients. *Aspergillus* is common in the environment, but the disease is rare and essentially confined to patients with significant underlying immunosuppression and locates primarily in the lungs or sinus, but can affect any organ. Invasive aspergillosis (IA) is one of the most difficult infections to treat, with mortality approaching 90 % in the most severely immunocompromised patients, despite available treatment.

Amphotericin B (AmB) is the current standard treatment of IA although the outcome remains poor. Alternative therapies have been developed with reduced toxicity compared to AmB: lipid formulations of amphotericin B (lipAmB) and itraconazole. There are no published placebo-controlled trials in patients failing prior antifungal therapy and overall very few randomised active comparator controlled studies. Efficacy (complete or partial) of approximately 40 % has been demonstrated in open-label, non-comparative or emergency-use of protocols of the lipAmB in patients refractory to or intolerant of initial therapy. The role of itraconazole as first-line therapy in immunocompromised patients with acute IA has been questioned and empirical data are still sparse. Furthermore, itraconazole is associated with multiple interactions with medicinal products mediated by the cytochrome P-450 enzyme system. As a result, there is a clear need for new, less toxic therapies active against *Aspergillus*.

### 2. Part II: Chemical, pharmaceutical and biological aspects

#### • Composition

The finished product is presented as a lyophilised sterile powder to be reconstituted and diluted prior to intravenous administration. It is available as 50 mg and 70 mg powder for concentrate for solution for injection and as 50 mg powder for solution for injection (presented in the transfer set vial).

The other ingredients in the formulation are: acetate, sucrose, mannitol, sodium hydroxide and water for injections. Argon is also used as an inert gas, prior to stoppering.

For all presentations, the powder is contained in a Type I glass vial closed with a butyl rubber stopper. The conventional vial is sealed with a 20 mm one piece aluminium seal with plastic flip-off cap. The transfer set vial is sealed with a multi-component cap that provides for a direct connection to the diluent bag.

- **Active substance**

The active substance, caspofungin (as the diacetate salt) is a semi-synthetic macrocyclic lipopeptide synthesised from a fermentation product. Synthesis involves fermentation, followed by isolation and purification of an intermediate containing all 16 chiral centres in the correct configuration, and a subsequent three step chemical modification, which has been shown to be stereo-retentive with regard to this configuration.

The structure of the molecule has been confirmed by the usual spectroscopic techniques. Investigations into the solid-state properties revealed no evidence of polymorphs or solvates.

#### Specification

Theoretical and found impurities formed during fermentation and synthesis have been investigated by means of a validated gradient HPLC method. Impurities are quantified and the specified levels are justified from a safety point of view. The specification includes tests for assay, acetate ion, residual solvents, water and sulphated ash. Identity is confirmed in terms of specific optical rotation, IR spectrum and HPLC profile versus reference.

Batch analyses of three commercial scale batches confirm satisfactory uniformity and compliance with the agreed and justified specification.

#### Stability

Caspofungin diacetate in the solid state is unstable even under moderate refrigeration and therefore must be stored at -70°C. Stability studies at this temperature for up to 24 months indicate no evidence of significant degradation. The retest period and the containers have been justified.

- **Other ingredients**

The other ingredients in the formulation are sucrose, mannitol, glacial acetic acid, sodium hydroxide, and water for injections, and these all comply with Ph. Eur. monographs. There are no ingredients of animal origin which give rise to concerns related to TSE.

- **Product development and finished product**

Caspofungin is not absorbed orally and therefore a formulation for intravenous infusion has been developed.

One main focus in the development work has been on optimising the stability of the product (minimising chemical degradation of the substance during manufacture and storage). A lyophilised formulation was found to be an alternative to other formulations since the active substance demonstrates inadequate stability both in solution and as a dry powder. The stability of caspofungin diacetate in buffered solution depends on the type of buffer used.

Due to the thermal instability of the active substance (degradation and decomposition) it is not possible to terminally sterilise the solution by autoclaving. Gamma irradiation was also investigated but was shown to be unsuitable. Aseptic filtration process is therefore the only viable option.

A chilled buffered solution of caspofungin acetate is filtered through sterilising filters in series. The filtered solution is filled into pre-sterilised 10 ml glass vials and partially stoppered with pre-sterilised siliconised butyl rubber stoppers. To each presentation 0.05 ml of the filtered solution is added as an overage to account for filling variations. After lyophilisation the stoppers are fully sealed under argon and stored at 2 to 8°C. Process and filter validation data were provided and found to be satisfactory.

#### Product Specification

The product release specification focuses on degradation products observed during the stability studies. In addition to the assay (HPLC), the other tests and limits are relevant for a product of this

type: completeness and clarity of solution; particulate matter; identification of active substance; uniformity of content; pH; moisture; endotoxins; sterility (Ph. Eur.).

Batch analysis data for the 50 mg and 70 mg presentations indicate satisfactory uniformity and compliance with the agreed, justified specification. The assay limit takes into account the above-mentioned overage for all presentations, as well as a 5 % overfill for the conventional vials. The conventional vial and the transfer set vial presentations therefore have different specifications for assay.

A separate product shelf-life specification has been defined, based on stability results, and is similar to the release specification, but with slightly adjusted limits for degradation products.

- **Stability of the Product**

Data provided from stability studies, utilising a reduced sampling matrixing design, have demonstrated the stability of the product when stored at 2 – 8°C in the vials intended for marketing. Characteristics studied include all the tests in the specification, under conditions of 5°C/ambient relative humidity and 25°C/60 % relative humidity for up to 24 months depending on the presentation. The improved product stability compared to the pure active substance stability may be explained by the stabilising effects of the formulation ingredients. Different stability data were provided in support of the shelf-life of the conventional vial (24 months) to that of the vial with the integral transfer set (18 months), and the resultant difference in shelf-lives is reflected in the Summary of Product Characteristics.

Stability after reconstitution

The results from reconstitution/dilution studies in Water for Injections, Saline solutions and Lactated Ringer's solution in commercially available PVC bags indicate chemical stability of the reconstituted/diluted product at 25°C, and these conditions and the maximum storage times are as defined in the SPC. Dextrose 5% solution for injection is not recommended as a diluent.

### **3. Part III: Toxicopharmacological aspects**

#### **Pharmacodynamics**

##### Mechanism of action

Caspofungin, a semi-synthetic lipopeptide of the echinocandin family, presents a new mode of action compared to other antifungal agents. It is based on the inhibition of 1,3-β-D-glucan synthesis, a critical process in the formation of the structural cell wall in some pathogenic fungi such as *Candida albicans* and *Aspergillus fumigatus*. Caspofungin prevents enzymatic transfer of glucose from UDP-glucose into 1,3-β-D-glucan in the membrane fractions from *A. fumigatus* and *C. albicans* with inhibitory concentration 50 % values of 9.6 and 0.6 nM, respectively. A direct correlation between enzyme inhibition and antifungal activity *in vitro* or *in vivo* has not been established. Mammalian cells lack 1,3-β-D-glucan, indicating fungal specificity of action.

The antifungal activity of caspofungin has been extensively studied both *in vitro* and *in vivo* using primarily mouse models.

- ***In vitro* studies**

*In vitro*, susceptibility testing of clinical isolates and standard strains showed that caspofungin has activity against a range of yeasts, fungi and molds. It has, in general, comparable or lower minimal inhibitory concentration (MIC) values than AmB against *Candida* and *Aspergillus*.

The testing on *Aspergillus* presented particular problems partly due to its existence as a mixed cell population and the absence of standardised *in vitro* susceptibility testing method for echinocandins. The proposed National Committee for Clinical Laboratory Standards (NCCLS) reference method M38-P was used for *Aspergillus* species, which is acceptable. In a study on 102 clinical isolates, using the endpoint of substantial inhibition of visual growth defined according to that method, at 24 hours,

the MIC<sub>90</sub> (MIC of 90 % of tested isolates) ranged from 0.2 to 0.5 µg/ml (0.15-0.4 µM). A correlation between MIC values and clinical outcome (favourable/unfavourable) has not been established.

Extensive investigations suggested that caspofungin is not traditionally fungicidal or fungistatic against *Aspergillus fumigatus* but is fungicidal to the hyphae at its tips and branch points where cell growth and division occur. Indeed *in vitro*, during a long term incubation study, the mass fungal increased under caspofungin exposure which could suggest a fungistatic activity. The morphology of hyphal growth appeared different in the presence of caspofungin compared with controls and the subapical growth forms did not cause deaths in chronically immunosuppressed mice up to 35 days post treatment. This implied a different pathogenicity, but the clinical relevance of these aberrant hyphae is unknown. The development of conidiophores observed in *in vitro* cultures during caspofungin exposure was not considered clinically relevant. Other *in vivo* studies, using histology and fungal organ burden, revealed a fungicidal activity of caspofungin comparable to amphotericin B. Caspofungin has, however, a clear fungicidal activity against *Candida* spp. with MIC values ranging from 0.25 to 8 µg/ml, generally comparable with amphotericin B. Values increased up to 4-fold in the presence of 50 % human serum in RPMI medium, but using another medium no significant effect of serum was recorded. Corresponding data for *Aspergillus* are not available. Evaluation for a possible correlation between MIC and treatment outcome is ongoing in the caspofungin *Candida* studies.

As expected, based on a different mechanism of action, caspofungin was active against azole-resistant strains of *Candida* and *Aspergillus*. Additionally, *Candida* and *Aspergillus* isolates, resistant to AmB were still susceptible to caspofungin. There are currently too limited data on the development of resistance to caspofungin but the applicant committed to further monitor this issue during the post-authorisation phase. The mechanism of resistance seemed linked to a mutation in the FKS gene of the fungus, presumed to be glucan synthase.

Caspofungin was inactive against *Fusarium* spp. and *Rhizopus arrhizus* and, as other glucan synthesis inhibitors, had insignificant activity against *Cryptococcus neoformans*.

- *In vivo* studies

Studies in animal models were generally consistent with clinically relevant activity of caspofungin. Animal models included disseminated and pulmonary aspergillosis, disseminated and oropharyngeal/gastrointestinal candidiasis, cryptococcosis, histoplasmosis and *Pneumocystis carinii* pneumonia.

#### Aspergillosis

*Aspergillus fumigatus* and *Aspergillus flavus* were tested in animal models.

Caspofungin given by intraperitoneal route was protective against disseminated aspergillosis in immunocompetent and immunocompromised mice. The ED<sub>90</sub> in mice lacking C'-5 were 0.44 and 0.21 mg/kg/dose for caspofungin and AmB, respectively. The effective daily dose in this model tended to be greater when given once daily in comparison to twice daily, although not remarkably increased (0.44 mg/kg *versus* 0.24 mg/kg). When therapy was delayed for 24 hours in mice chronically immunosuppressed with cyclophosphamide, the ED<sub>90</sub> were 0.486- >1 mg/kg/dose and 0.753- >1 mg/kg/dose for caspofungin and AmB, respectively. The day 21 ED<sub>50</sub> in a monoclonal antibody-induced neutropenic mouse survival model of aspergillosis were 1.05 and 0.85 mg/kg for caspofungin and AmB, respectively. Caspofungin increased the survival in mice with disseminated aspergillosis with ED<sub>50</sub> equivalent to 0.02 mg/kg intravenously.

Neither caspofungin nor AmB was protective in a mouse model of disseminated aspergillosis induced by *A. flavus*. Further, none of them were effective in a pulmonary *A. fumigatus* mouse model at doses of 0.375 mg/kg bid, administered by intraperitoneal route. Data presented in an abstract indicated, though, that caspofungin has activity at higher doses against pulmonary aspergillosis in rat.

#### Candidiasis

Studies in mouse survival models of disseminated candidiasis and in target organ assays were consistent with significant anti-candidiasis activity of caspofungin, overall comparable to or better

than AmB. The day 21 ED<sub>50</sub>s ranged from 0.07-0.12 mg/kg for caspofungin and 0.19-0.42 mg/kg for AmB. Loss of activity was evident in 5-fluorouracil neutropenic mice and using an azole resistant strain of *C. albicans*.

### Other

Caspofungin was effective against *Pneumocystis carinii* pneumonia in corticosteroid-immunosuppressed rats and mice, with ED<sub>90</sub> approximately of 0.02 mg/kg.

In contrast to AmB, caspofungin was not effective in a mouse model of cryptococcosis.

Caspofungin prolonged survival at dose of 0.05 mg/kg/day in a mouse model of histoplasmosis induced by *Histoplasma capsulatum*.

- Pharmacodynamic interactions

*In vitro* studies showed a synergistic activity between caspofungin and AmB against *Cryptococcus neoformans* and *A. fumigatus* and revealed no antagonistic activity against *C. albicans*. Combination studies were not conclusive with regard to additive or synergistic activity between caspofungin and AmB or fluconazole in mouse models. However against *A. fumigatus*, the combination of caspofungin (0.008 mg/kg) with AmB (0.125 mg/kg) produced an improvement in mice survival over the two agents taken alone.

In rats, ketoconazole (25 mg/kg orally) had no effect on the disposition of caspofungin (2 mg/kg i.v.) whereas indinavir (20 mg/kg orally) tended to increase the plasma levels of caspofungin although not significantly.

AmB (0.5 mg/kg orally) had no effect on the steady-state pharmacokinetics of caspofungin when co-administered in rats and similarly caspofungin had no effect on AmB pharmacokinetics.

In rats also, cyclosporine (10 mg/kg, p.o.) increased by about 27 % C<sub>min</sub> values of caspofungin when given at 2 mg/kg, iv and by 16 % AUC levels. There was a modest decrease in the liver uptake of caspofungin. Further studies *in vitro* showed that cyclosporine had no effect on the unbound fraction of caspofungin in liver homogenate and thus did not seem to displace caspofungin binding.

Further studies to evaluate the combination of caspofungin with other antifungal agents *in vitro* and in animal models are ongoing, the results of which will be submitted as part of follow-up measures to be fulfilled post authorisation.

### General and safety pharmacology programme

Although general pharmacodynamic studies were not conducted strictly according to Good Laboratory Practices principles, they were adequately performed. Overall, caspofungin was well tolerated. In dog and mouse, no relevant effect on the respiratory, renal, gastrointestinal or central nervous systems were in evidence at doses up to 5 mg/kg. Single intravenous bolus injection of  $\geq 3$  mg/kg in rat produced adverse cardiovascular effects, overall consistent with endogenous histamine release. In monkey, infusion of 16 mg/kg, but not 8 mg/kg, also caused adverse cardiovascular effects. No significant changes in QTc interval were reported in dogs. However to exclude any potential risk of QT prolongation associated with caspofungin, the applicant undertook to conduct further studies, the results of which will be submitted post-authorisation.

### Pharmacokinetics

The pharmacokinetics profile of caspofungin was evaluated in rats and monkeys following intravenous administration. Caspofungin was initially measured by HPLC method using fluorescence detection (lower limit of quantification 100 ng/ml) while radio-immuno assay method was used in later studies (lower limit of quantification 10 ng/ml).

- Absorption

The oral absorption was very poor in rats, with oral bioavailability less than 0.2 % after doses of 50 mg/kg. After single doses administered intravenously in rats over a dose range of 0.5 to 5 mg/kg, a approximate linear relationship was noted between the area under the concentration-time curve (AUC) and dose. The AUC was comparable after single dose ( $4813 \pm 451 \mu\text{g} \times \text{min}/\text{ml}$ ) and multiple doses ( $4061 \pm 398 \mu\text{g} \times \text{min}/\text{ml}$ , day 10) of 2 mg/kg for up to 21 days. In monkeys, the terminal half-life appeared to increase with time and after multiple doses (5 mg/kg) for 14 days there was evidence of accumulation with an increase in the  $C_{\text{min}}$  from 2.4  $\mu\text{g}/\text{ml}$  (day 2) up to 5.6  $\mu\text{g}/\text{ml}$  (day 10). The steady state appeared to be reached within 10 days.

- **Distribution**

Distribution of  $^3\text{H}$ -casprofungin in rats after single intravenous dose (2 mg/kg) was extensive with highest amounts in kidney, lung, liver and spleen. The tissue radioactivity peaked within 2 hours in most tissues and within 24 hours in the liver where it then decreased slowly, with about 3 % remaining at day 12. This suggests that the processes of hepatic uptake and elimination of casprofungin are very slow, and that the equilibration of the compound between blood and liver tissue is not established rapidly. Results from an *in situ* rat liver perfusion preparation were consistent with the hypothesis that the hepatic uptake of casprofungin is a 2-step process involving an initial rapid binding of casprofungin to the cell surface that is followed by a slow mechanism of transport into the cell. Casprofungin is neither a substrate nor an inhibitor for P-glycoprotein.

Casprofungin was extensively bound to rat, monkey and human plasma proteins. The free fraction accounted for 4.1 % in rat, 1.3 % in monkey and 3.5 % in humans. The extent of binding was concentration independent up to 100  $\mu\text{g}/\text{ml}$ . Irreversible binding that increased with time, to monkey and human plasma proteins, was detected. The binding to plasma proteins proceeded mainly via an imine reaction, but also involved a nucleophilic addition mechanism. Casprofungin derived adducts with human  $\beta$ -endorphin were reported. The extent of covalent binding to liver protein will be further investigated.

Small fraction of casprofungin binds also to the plasma low density lipids components (about 3 % in rat, 0.5 % in monkey and 2 % in human).

The major systemic metabolite, L-747969, was also highly protein bound with a free fraction of 1 % in monkey and 2 % in human.

Distribution into erythrocytes was limited with a blood/plasma ratio of approximately 0.72 and casprofungin does not appear to cross the blood-brain barrier readily.

- **Metabolism**

Qualitatively, all major metabolites of casprofungin detected in humans were also found in rats and monkeys. The metabolism pathway included peptide hydrolysis and N-acetylation in all species. The CYP enzyme system was not involved. The ring-opened product L-747969 was a major component in plasma and highly protein bound. Two major metabolites, M1 and M2, were detected in urine of rat, monkey and human. The potential antifungal activity of the metabolites and intermediates is currently unknown.

- **Elimination**

Elimination was polyphasic with a half-life of 2.75 days for casprofungin in monkey plasma and approximately 12 days in humans and monkeys for total radioactivity. An effective half-life of approximately 4.3-8 hours in rat and monkey was calculated based on plasma concentrations exceeding  $\text{MIC}_{90}$  of 0.5  $\mu\text{g}/\text{ml}$ .

Casprofungin was excreted via urine and faeces, and about 70 % of the dose was recovered after 28 days. The low recovery is consistent with the prolonged excretion phase of casprofungin as characterised by a 12-day half-life of casprofungin-related materials in plasma. When  $^3\text{H}$ -casprofungin (2 mg/kg) was administered intravenously to rats, 42 % of the dose was excreted into urine and 29 % into the faeces over a 12-day collection period. In bile duct cannulated rats, 3 % of the dose was found in the bile, mainly as unchanged compound. The same pattern of excretion was found in monkey, mouse, rabbit, and human. The majority of the radioactivity in the initial urine of all species was in the form of unchanged drug. At later time points, the major fraction of the radioactivity consisted of

predominantly polar metabolites (dihydroxyhomotyrosine, its N-acetyl derivative, and an unidentified minor metabolite).

## **Toxicology**

The toxicological profile of caspofungin in the diacetate form has been evaluated in mice, rats, monkeys and rabbits. Based on pharmacokinetics data, species selected were considered as relevant models, although fewer data were available in mice and rabbits. All main studies were performed according to Good Laboratory Practices.

A preformulated lyophilised material that contains impurities/degradates at levels that qualify to clinical specifications was also used in some repeated dose toxicity, reproduction toxicity and genotoxicity studies.

- **Single dose toxicity**

Death in acute toxicity studies occurred very rapidly. Single intravenous administration of doses equal to or superior to 25 mg/kg in mice and 50 mg/kg in rats, resulted in death. Clinical signs prior to death included tremors, decreased activity and bradypnea in mice and decreased activity, bradypnea, tail discoloration, and swelling and necrosis at the injection sites in rats. Some of these signs were consistent with endogenous histamine release.

- **Repeat dose toxicity**

The toxicity of caspofungin after repeated intravenous doses was evaluated in rats and monkeys for up to 27 weeks. The maximum doses were 7.2 mg/kg/day in rats and 8 mg/kg/day in monkeys, which represented approximately 7-fold the proposed clinical dose. In rats and monkeys, these doses resulted in systemic exposure levels approximately 1.5 to 2-fold and 3 to 7-fold higher than the expected clinical exposure, respectively. The toxicokinetic studies revealed that the exposure in rats and monkeys at the NOEL (2 mg/kg/day) was close to the human exposure during treatment.

The major findings, that are discussed in the following paragraphs, include:

- Clinical signs due to histamine release in rats
- Increase in liver transaminase levels in monkeys
- Reactions at injection site in both species

### *Histamine release*

In rats, clinical signs such as ataxia, decreased activity, recumbency, hyperemia and swelling of extremities were consistent with histamine release. In the 5 and 14 week studies, these signs were observed only in the high dose group (5 mg/kg/day) whereas in the 27-week study it occurred in all treatment groups. It has been established that a single bolus intravenous dose of caspofungin may cause signs of histamine release in monkeys, however, no such signs occurred in the repeat dose studies of 5 to 27 weeks duration where caspofungin was infused over a 20-minute period at doses up to 6 mg/kg/day. Supplementary *in vitro* studies supported a role of histamine release in the reactions observed. In peritoneal mast cells from rats, caspofungin induced histamine release which was detectable at 1 µg/ml, degranulation being almost complete at 100 µg/ml. The same concentration had no significant effect on human basophil and lung mast cells, whereas a small effect (about 10 % degranulation) was detected in skin mast cells.

### *Increase in liver transaminase levels*

In monkeys, liver was the primary target of toxicity in all studies. Effects consisted mainly of increases in liver transaminase levels (AST and ALT). The NOEL for this effect was 2 and 1.5 mg/kg/day, the lower value being obtained in the 27 week study. In one 5-week study in monkeys at doses which produced exposures approximately 4 to 6 times those seen in patients treated with a 70 mg dose, scattered small foci of subcapsular necrosis were observed microscopically in the livers of some animals (2/8 monkeys at 5 mg/kg/day and 4/8 monkeys at 8 mg/kg/day); however, this histopathological finding was not seen in another study of 27 weeks duration at similar doses. Increases in transaminase levels generally correlated with the hepatic levels of caspofungin since, for the same 5 mg/kg/day dose, the hepatic level of caspofungin was twice greater in monkeys than in

rats, in which no liver transaminase increases or treatment-related hepatic histopathologic findings occurred.

#### *Reactions at injection site*

The most prominent reaction in both rats and monkeys was injection site changes characterised by necrosis, thrombosis, oedema, focal discoloration of vein and fibroplasia. The severity of these effects was reduced with a saline flush before and after infusion. The NOEL for injection site changes ranged from 1.8 to 2 mg/kg/day in rats and was 3 mg/kg/day in monkeys in 27-week studies.

#### *Additional findings*

A tendency for increased triglycerides was noted in rabbits and pregnant rats.

No relevant toxicological changes were noted in juvenile monkeys given 5 mg/kg/day for 5 weeks.

Overall pronounced toxicity was not manifest in repeated dose toxicity studies but the maximum dose might have been limited by methodological problems associated with long-term intravenous administration and by the occurrence severe reactions coupled to histamine release in rats. The NOELs identified did not attain many multiples over expected clinical levels on a dose or systemic exposure basis.

- Genotoxicity

Caspofungin was not genotoxic in a standard battery of *in vitro* and *in vivo* tests.

- Carcinogenicity

No carcinogenicity studies have been conducted with caspofungin in view of the expected short duration of treatment (less than 6 months). This is consistent with the current international guidelines on carcinogenicity testing.

- Reproduction toxicity

Studies were conducted in rats and rabbits using lyophilised formulation given intravenously with maximum doses of 5 and 6 mg/kg/day, respectively. Toxicokinetic studies were performed in pregnant rats and rabbits using doses of 5 mg/kg/day administered intravenously. This dose produced systemic exposure levels of approximately 203-212 µg x h/ml. In comparison with the human systemic exposure at a dose of 70 mg (AUC<sub>0-24h</sub> approximately equivalent to 150 µg x h/ml), the margins of exposure are low and in most cases identified NOELs are likely to be below expected human exposure.

In rats, no effect on either male or female fertility was apparent. The NOEL was determined > 5 mg/kg/day.

In an embryo-foetal development study in rats, maternal toxicity was limited to signs of histamine release and foetal survival was not affected by caspofungin. In the 5 mg/kg/day group, there was a slight decrease in foetal weights as well as an increased incidence of cervical ribs and incomplete ossification of torso (vertebra, sternebra) and skull bone. When considering foetuses with skeletal malformations and litters affected, there seemed to be an increased incidence in the high dose group: 1 foetus/1 litter in control group versus 6 foetuses/4 litters in high dose group (including one foetus with multiple malformations). Individual malformations were stated to be within historical control ranges.

In an embryo-foetal study in rabbits, slight increase in peri/post-implantation loss was apparent but the relation to treatment was equivocal as values remained within the historical control data. There was no effect on foetal survival or any evidence of teratogenicity, indicating a NOEL > 6 mg/kg/day.

Treatment with caspofungin seemed devoid of any significant effect in the peri/post natal study in rats, indicating a NOEL > 5 mg/kg/day.



Caspofungin crossed the placenta in rats and rabbits. At 24 hours post-dose (5 mg/kg/day), the mean foetal concentrations were 18 % and 29 % of the maternal plasma concentration, respectively in the two species. In addition, caspofungin excreted into milk of lactating rats (milk concentration was 13 % of plasma concentration). In view of these results and in the absence of human data, caspofungin should not be used during pregnancy unless clearly necessary and should not be used in lactating women, as mentioned in the Summary of Product Characteristics.

- Local tolerance

Caspofungin was less hemolytic than AmB with minimum lytic concentrations of 450 µg/ml in washed human blood. Caspofungin was a mild skin irritant in the rabbit (500 mg/site), but severely irritating to the eye in an *in vitro* test (20 % (w/v)).

- Other toxicity

In the toxicity studies using the lyophilised formulation containing degradation products at levels at least equivalent to the formulation intended for marketing, there was no indication that the presence of any degradates or impurities altered the toxicity profile of caspofungin.

No specific studies have been performed to evaluate the immunogenic potential of caspofungin, however there was no evidence for any immunogenicity potential in the repeat dose toxicity studies in rats or monkeys.

- Ecotoxicity/Environmental risk assessment

An assessment of the environmental risk was performed and no significant risk to the environment related to the use of caspofungin is anticipated.

#### **4. Part IV Clinical aspects**

The initial clinical development programme for caspofungin focused on the treatment of documented *Aspergillus* and *Candida* infections in adult patients. It included 12 pharmacokinetic studies and 3 phase II studies carried out in patients with oropharyngeal and oesophageal candidiasis. Based on the preliminary efficacy and safety data, confirmatory phase III studies were initiated to evaluate the clinical benefit of caspofungin in the treatment of invasive aspergillosis in patients refractory to or intolerant of standard therapy. The clinical programme in this indication was designed according to the scientific advice provided by the CPMP in December 1999.

In addition, confirmatory trials enrolling patients with candidiasis were initiated. Since the treatment of *Candida* infections was an indication not sought at the time of the submission of the application, the results from these studies could only be considered as supportive.

All the studies were conducted in accordance with agreed International Ethical Principles and Good Clinical Practices standards.

The approved indication is for treatment of invasive aspergillosis in adult 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.

#### **Clinical pharmacology**

##### **Pharmacodynamics**

- Mechanism of action

As already mentioned in section 3 of this document (part III pharmaco-toxicological aspects), caspofungin, a semi-synthetic lipopeptide of the echinocandin family, presents a new mode of action compared to other antifungal agents. It is based on the inhibition of 1,3-β-D-glucan synthesis, a

critical process in the formation of the structural cell wall in some pathogenic fungi, including *Aspergillus* and *Candida*.

- Pharmacokinetics/Pharmacodynamics relationship

The relationship between pharmacokinetic parameters ( $AUC_{0-24h}$ ,  $C_{1h}$  and  $C_{24h}$ ) and treatment outcome (favourable/unfavourable) was evaluated in a population pharmacokinetic/pharmacodynamic analysis including 142 candidiasis patients who received daily doses of caspofungin (35 mg, 50 mg or 70 mg). A similar analysis was performed for patients with aspergillosis receiving a 70 mg bolus dose followed by 50 mg once daily. A relationship between pharmacokinetic parameters and treatment outcome could not be defined for caspofungin. In candidiasis patients, increased exposure ( $C_{24h}$ ) seemed associated with an increased rate of favourable response, whereas such relationship could not be established in patients with IA. Although it is likely to be difficult to establish a PK/PD relationship for caspofungin, considering the importance of many additional factors, such as immune function, the applicant committed to further investigate it as part of follow-up measure to be fulfilled post-authorisation.

### **Pharmacokinetics**

- General

Caspofungin pharmacokinetics was assessed in 12 pharmacokinetic studies conducted in healthy volunteers, in patients with renal or hepatic impairment and in patients with oesophagitis candidiasis and severe immunosuppression. Of the 312 subjects enrolled, 274 received caspofungin.

In addition, two population pharmacokinetic studies were performed based on phase II studies (P003, P004 and P007) involving patients with oropharyngeal and oesophageal candidiasis and the non comparative *Aspergillus* salvage study (P019).

Caspofungin was administered intravenously as an infusion over 60 minutes in all pharmacokinetic studies. Single doses ranging from 5 to 100 mg and multiple doses ranging from 35 to 70 mg once daily for up to 21 days were administered. All the analytical methods were adequate and a three compartmental model was selected to describe the pharmacokinetic profile of caspofungin.

- Absorption

As caspofungin has been developed for parenteral use only, the oral bioavailability was not determined.

Caspofungin displayed linear pharmacokinetics after single dose administration ranging from 5 to 100 mg. At the end of a 1-h infusion of 70 mg caspofungin, plasma concentrations ( $C_{1h}$ ) ranged usually from 9.5 to 12  $\mu\text{g/ml}$ , and 24 h later, plasma concentrations ( $C_{24h}$ ) ranged from 1 to 2  $\mu\text{g/ml}$ .  $AUC$ ,  $C_{1h}$  and  $C_{24h}$  displayed marked inter-individual variability (coefficient of variation ~30 %). Upon multiple dosing, caspofungin pharmacokinetics were moderately non-linear, with increased accumulation as the dose increased. There was a dose dependency in the time to reach steady state in healthy volunteers.

- Distribution

Following administration of a single intravenous dose, plasma levels of caspofungin declined in a polyphasic manner, with a rapid  $\alpha$  phase, a dominant  $\beta$  phase ( $t_{1/2\beta}$  ranged between 9 to 11 hours) and a long terminal  $\gamma$  phase ( $t_{1/2}$  approximately 45 h). 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 was slow, illustrated by a low plasma clearance (10-12 ml/min), and it peaked at 1.5 to 2 days postdose when 92 % of the dose was distributed into tissues.  $V_c$ ,  $V_{ss}$ ,  $V_z$  were estimated to be about 4 l, 10 l and 25 l respectively. It is likely that only a small fraction of the caspofungin taken up into tissues returns to plasma as parent compound. This suggests that the free caspofungin concentrations in plasma and tissue essentially never reach distribution equilibrium and that the elimination occurs in the absence of distribution equilibrium.

Caspofungin is highly bound to plasma proteins (97 %). The blood/plasma ratio was 0.74 indicating a limited distribution to erythrocytes.

The distribution of caspofungin into the brain of uninfected animals (rats and mice) was low, but data from preclinical models of disseminated candidiasis showed sterilisation of the brains of mice treated with caspofungin.

- **Metabolism**

Caspofungin undergoes spontaneous degradation to the ring-opening intermediate compound L-747969, which is the predominant component of extractable plasma radioactivity 5 to 20 days following a single dose. *In vitro*, it was shown that two reactive intermediates are formed during the degradation of caspofungin to L-747969 and that they may form covalent adducts to plasma proteins. Further metabolism appears to proceed through peptide hydrolysis to constituent amino acids or their degradates and subsequent N-acetylation. Two polar metabolites (M1 and M2) were identified as dihydroxyhomotyrosine and its N-acetyl derivative, respectively. All the metabolites found in humans were also present in animals. Caspofungin is not metabolised through cytochrome P450 system but the enzymes involved have not been identified.

- **Elimination**

After administration of <sup>3</sup>H-caspofungin, the terminal elimination half-life of radioactivity was 12 to 15 days. Unchanged drug constituted the majority of the radioactivity in plasma and urine during the first 24 to 30 h after administration. Recovery was only 75 %: 41 % of the dose was recovered in urine, predominantly in the form of the polar metabolites (M1 and M2) and 34 % in faeces during 27 days. Renal excretion of unchanged drug represents only 1.4 % of the total dose. There was no information regarding the metabolites in faeces, but that was considered acceptable in the context of the applied indication.

Modest but statistically significant reductions (20 to 25 %) in C<sub>1h</sub> were seen in patients with candidiasis compared to healthy volunteers after multiple doses of 50 and 70 mg. A small reduction in AUC<sub>0-24</sub> was found (10 % increase at 50 mg to 12 % decrease at 70 mg). There was a trend for greater C<sub>24h</sub> compared to healthy volunteers (6 % and 11 % increases at 50 and 70 mg respectively).

Limited data showed that the pharmacokinetics profile of caspofungin in patients with IA appears similar to the one obtained in patients with candidiasis.

In the population pharmacokinetic studies in patients with candidiasis, weight was found to influence statistically significantly the AUC<sub>0-24</sub>, C<sub>1h</sub> and C<sub>24h</sub>. There was a clear tendency towards reduced exposure (C<sub>24h</sub>) in patients weighing > 70-80 kg. The average exposure in a patient weighing 80 kg was predicted to be about 23 % lower than in a patient weighing 60 kg. This finding, together with the inter-individual variability raised the question of establishing a weight-based adjustment of the maintenance dose to ensure adequate exposure in all patients.

- **Special population**

*Patients with hepatic impairment*

Two studies were performed to evaluate the potential effect of caspofungin in patients with hepatic impairment. In a single dose study (70 mg dose), AUC increased by 55 % in patients with mild impairment (Child Pugh score 5 to 6) and by 76 % in patients with moderate impairment (Child Pugh score 7 to 9). In a multiple doses study (70 mg loading dose followed by 50 mg daily), a less pronounced effect of mild hepatic impairment on caspofungin pharmacokinetics was observed. On Day 1, AUC was only 15 % increased compared with normal subjects. On the basis of these data, no dosage adjustment is recommended in patients mild hepatic impairment. The protocol of the multiple doses study was amended to evaluate the effect of a maintenance dose of 35 mg in patients with moderate hepatic insufficiency. Preliminary results showed that a reduction of the maintenance dose to 35 mg daily provided an AUC similar to that observed in subjects with normal hepatic function receiving 50 mg daily. Therefore a reduction of the maintenance dose to 35 mg daily was considered adequate in this population as recommended in the Summary of Product Characteristics.

Currently there is no data to recommend any dosage adjustment in patients with severe hepatic impairment, and therefore caspofungin should be used with caution in this population as a higher exposure than in moderate hepatic insufficiency is expected in severe hepatic insufficiency.

*Patients with renal impairment*

The influence of renal function on caspofungin pharmacokinetics was evaluated in a specific study (after single 70 mg dose) in 36 patients with different degree of renal function. Caspofungin pharmacokinetics were unchanged in mild renal impairment while clearance decreased in moderate, severe and end stage renal disease. An increase in AUC of 31, 49 and 30 % was observed respectively in moderate, severe and end stage renal disease. Caspofungin was not cleared by dialysis.

In the population pharmacokinetic study in patients infected with aspergillosis (P019), there was a moderate increase in mean exposure in the groups with different degree of renal impairment. However, the inter-individual variability in caspofungin plasma concentrations is increased in these patients. Overall, the increase was considered modest and therefore no dosage adjustment in these patients is recommended in the Summary of Product Characteristics.

The pharmacokinetics profile of caspofungin has not yet been evaluated in children or adolescents.

Elderly patients had a 30 % increase in AUC<sub>0-24h</sub> and C<sub>24h</sub> due to slower elimination, however, no dosage adjustment is considered necessary. There was a small effect of gender on the pharmacokinetics of caspofungin, but it was considered insufficient to recommend any dosage adjustment. Race (Caucasian, Black, Hispanic and Mestizo) was not identified as a covariate influencing the pharmacokinetics of caspofungin.

- Interaction studies

As already mentioned, *in vitro* and *in vivo* data showed that caspofungin is not metabolised by CYP isoforms, and is neither inhibitor/inducer of CYP450 isoenzymes nor a substrate for P-glycoprotein. Potential interactions between caspofungin and antifungal or immunosuppressive agents that are most susceptible to be co-administered with caspofungin were evaluated in healthy volunteers. In these studies, caspofungin was administered for 10-14 days at clinical doses (50 mg daily with a 70 mg loading dose). The concomitant compounds were generally administered as a single dose. The main results are summarised below.

Caspofungin had no or little effect on amphotericin B (AmB), itraconazole and mycophenolate mofetil pharmacokinetics and vice versa. In the itraconazole interaction study, the incidence of rash seemed higher with combination treatment than with caspofungin alone, but the data were too scarce to draw firm conclusions. As already indicated, the combined treatment of caspofungin with other antifungal agents will be further evaluated *in vitro* and in animal models.

When caspofungin was co-administered with tacrolimus (2 x 0.1 mg/kg dose given 12 h apart), the pharmacokinetics of caspofungin was not affected while AUC and trough concentrations of tacrolimus were decreased by 20 and 26 % respectively. The mechanism for this interaction is currently unknown. Although the amplitude of the interaction is modest, it can be clinically meaningful and therefore monitoring of tacrolimus trough concentrations and dosage adjustment are recommended in the Summary of Product Characteristics.

Caspofungin had no or little effect on cyclosporin A (CsA) pharmacokinetics using either CsA as a single dose of 4 mg/kg or multiple doses of 2 x 3 mg/kg given 12 hours apart. On the other hand, increases in the caspofungin AUC and C<sub>24hr</sub> by about 35 % and 60 to 100 % were reported. A similar effect was observed in the preclinical studies. The combination resulted in transient elevations in liver enzymes (ASAT/ALAT) mostly between 1 and 2 fold the upper limit of normal (ULN), but some up to 3 times ULN. It was suggested that the mechanism of interaction involved the distribution of caspofungin into tissues rather than the metabolism of caspofungin. Further studies will be initiated before drawing definite conclusions on any dosage recommendations. In the meantime the combination should be used with caution and monitoring of the liver tests should be considered as indicated in the Summary of Product Characteristics.

A screening for other potential interactions was performed in the population pharmacokinetic analysis. Caspofungin concentrations were reduced during concomitant medication with CYP inducers in candidiasis patients. Preliminary results from an interaction study showed that rifampicin (600 mg daily) caused a 61 % increase in caspofungin AUC (90 % CI: 1.46-1.79) and 170 % increase in C<sub>24h</sub> (90 % CI: 2.206-3.31) on day 1 of the co-administration of the two substances (caspofungin

administered at 50 mg daily). Caspofungin trough levels gradually decreased and after 14 days of co-administration, rifampicin had limited effect on AUC (12 % increase; 90 % CI: 0.97-1.30) but trough levels were 30 % lower than in subjects who received caspofungin alone. The mechanism of this interaction could possibly be related to an initial inhibition of transport proteins followed by a subsequent induction. A similar effect could be expected with other substances that induce metabolic enzymes. In order to increase the trough levels during concomitant administration of inducers of metabolic enzymes, the increase of the daily dose of caspofungin to 70 mg, following the 70 mg loading dose should be considered as recommended in the Summary of Product Characteristics.

### **Clinical efficacy**

The efficacy of caspofungin in the treatment of invasive aspergillosis (IA) was evaluated in one non-comparative study involving adult patients, including patients with severe underlying diseases and immune dysfunction, who were refractory to or intolerant of standard therapies: the *Aspergillus* salvage study (Protocol 019).

In addition the results from a compassionate use study (Protocol 024/025) and from a historical control study (Protocol 028/029), which was closely modelled after the protocol study 019 and described the efficacy of standard antifungal therapy in IA, were provided.

Supportive efficacy data derived from randomised comparative Phase II studies in patients with oesophageal and/or oropharyngeal candidiasis. Supportive safety data included also results from the completed phase III study P020 (caspofungin versus fluconazole in the treatment of *Candida* oesophagitis), the ongoing phase III study P014 (caspofungin versus AmB in treatment of invasive candidiasis) and ongoing phase III study P026 (caspofungin versus lipid formulation of AmB in empirical treatment of fever and neutropenia).

The table 1 provides an overview of the clinical programme with caspofungin.

Table 1: overview of the clinical programme with caspofungin

Protocol/ Title/N	Phase	Major Entry Criteria	Treatment Daily Doses/Duration	Primary Efficacy Endpoints
<b>Efficacy in Invasive Aspergillosis</b>				
019 [P019] Invasive Aspergillosis Study n= 58 (+11)	IIb	Definite or probable <i>Aspergillus</i> infection, and refractory to or intolerant of standard antifungal therapy	Caspofungin 70 mg x 1 day, then 50 mg daily/variable	Resolution or clinically meaningful improvement in symptoms, signs, and radiographic or bronchoscopic abnormalities.
024/025 [P024] Compassionate Use Protocol (n=3)	III	Definite or probable <i>Aspergillus</i> infections; invasive candidiasis, oropharyngeal candidiasis, or oesophagitis and refractory or intolerant of standard antifungal therapy	Caspofungin 70 mg x1 day, then 50 mg daily/variable	Resolution or clinically meaningful improvement in symptoms, signs, and radiographic or bronchoscopic abnormalities.
028/029 [P028] Historical Control Study (n=206)	NA	Definite or probable <i>Aspergillus</i> infection treated between 1995-1998 with at least 7 days of standard antifungal therapy.	Minimum of 7 days of therapeutic doses of standard antifungal therapy	Resolution or clinically meaningful improvement in symptoms, signs, and radiographic or bronchoscopic abnormalities.
<b>Efficacy in Candidiasis (supportive studies)</b>				
003 [P003] Pilot <i>Candida</i> oesophagitis study (n= 128 )	IIa	Microbiologically documented <i>Candida</i> oesophagitis	Caspofungin 50, 70 mg daily <i>versus</i> Amphotericin B 0.5 mg/kg daily/14 days	Evaluation of symptoms and endoscopy.
007 [P007] <i>Candida</i> oesophagitis PK Study (n=14)	IIa	Microbiologically documented <i>Candida</i> oesophagitis	Caspofungin 50 mg, 70 mg daily/ 14 days	Pharmacokinetics in patients with fungal infections.

Protocol/ Title/N	Phase	Major Entry Criteria	Treatment Daily Doses/Duration	Primary Efficacy Endpoints
004 [P004] Dose-Response oropharyngeal Candidiasis or oesophageal Candidiasis Study (n=140)	IIb	Microbiologically documented oropharyngeal candidiasis or oesophageal candidiasis	Caspofungin 35, 50, 70 mg daily <i>versus</i> Amphotericin B 0.5mg /kg daily/ 10-14 days	Evaluation of symptoms and oropharyngeal exam or endoscopy.

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

### **Dose-response studies**

No formal dose-response study was performed to define the optimal dosage regimen of caspofungin in the treatment of IA.

The dosing regimen was selected based on an integration of data from *in vitro* susceptibility testing, animal models of IA and disseminated candidiasis, clinical pharmacokinetics in healthy volunteers and Phase II studies in patients with oropharyngeal and/or oesophageal candidiasis (studies P003 and P004 described in table 1). Single dose pharmacokinetic data in healthy volunteers demonstrated that the beta phase half-life of caspofungin was 9 to 11 hours, supporting the selection of a once daily dosing regimen.

The initial study (P003) showed that both doses of caspofungin (50 mg and 70 mg daily) were well tolerated and appeared at least as effective as AmB. No statistically significant difference could be observed between the two doses.

In the second study (P004), there was no evidence of dose-related toxicity over the range of doses tested (35 mg, 50 mg and 70 mg). All 3 caspofungin doses appeared at least as effective as AmB, and there was no evidence for increased efficacy for 70 mg dose as compared to 50 mg dose. Therefore the 50 mg daily dose was considered the appropriate dose for the subsequent clinical studies.

Based on *in vitro* susceptibility testing data, as presented in Pharmaco-toxicological part of this document, it was targeted to maintain plasma caspofungin levels above 1.0 µg/ml throughout the dosing interval. Pharmacokinetic data demonstrated that the 50 mg dose produced target trough levels below 1 µg/ml early in the course of therapy. On the other hand, a 70-mg loading dose followed by a daily dose of 50 mg produced caspofungin trough levels above 1.0 µg/ml from the first day of therapy and achieved steady state more rapidly. In addition, the population pharmacokinetics in Phase II oesophagitis studies suggested that caspofungin levels in patients were higher and more variable than levels seen in healthy volunteers and an increased exposure ( $C_{24h}$  and AUC) could be associated with an increased rate of favourable response.

Thus, the use of a 70 mg loading dose was recommended in the subsequent Phase II/III studies of invasive infections due to *Candida* or *Aspergillus*. The 40 % increase in the loading dose relative to the maintenance dose was consistent with the moderate level of accumulation observed in the pharmacokinetic studies. There are no data however on the maximum tolerated dose of caspofungin. Although the proposed dosage regimen (loading dose of 70 mg followed by 50 mg once daily) maintains mean trough concentrations above 1 µg/ml and have been shown safe and effective in the treatment of IA, concerns were raised. Indeed the target trough concentration of 1 µg/ml was insufficiently supported and the risk that patients with high body weight were undertreated could not be excluded since there was a clear tendency towards reduced exposure in patients weighing more than 70-80 kg. Additional simulations of the exposure obtained with different dosage regimens were presented during the oral explanation and subsequent written responses. Although the clinical benefit of increasing the maintenance dose in patients with higher body weights was not demonstrated, no increased safety risk associated with higher dosages were anticipated. As the serious nature of IA infection requires that precautions are taken to ensure adequate exposure in all patients, 80 kg was chosen as the appropriate cut-off weight at which to apply dose adjustment of the maintenance dose

(i.e. increasing from 50 mg q.d. to 70 mg q.d.). Protocols of some ongoing clinical studies have been amended to further define the adequacy of higher doses.

**Main study: *Aspergillus* salvage study (P019 + P019S)**

- Description of the study

This was a multicentre, open-label, non-comparative study to evaluate the safety, tolerability and efficacy of caspofungin acetate in the treatment of *Aspergillus* infections in patients who were refractory to or intolerant of AmB, lipid formulations of AmB or azoles. Sixty-nine patients were enrolled by 30-Apr-2000.

Patients were required to have documented infection (radiographic evidence plus culture, histopathology or antigen detection), and to have definite extrapulmonary aspergillosis and definite or probable pulmonary aspergillosis.

*Definite disease* was defined as a positive culture or histopathology from an invasive procedure plus appropriate clinical and radiographic findings.

*Probable pulmonary aspergillosis* required an appropriate clinical setting, radiographic abnormalities consistent with IA, and either positive cultures from sputum or bronchoalveolar lavage or repeatedly positive tests for the detection of antigen (galactomannan ELISA) or DNA polymerase chain reaction (PCR). Patients were upgraded to definite disease if at a later surgical procedure or autopsy, they were found to have *Aspergillus* by histopathology.

These definitions of infection are modelled according to the Mycoses Study Group (MSG) criteria and are consistent with the new joint recommendations regarding the definitions for invasive fungal infections that have been developed by the MSG and the European Organization on Research and Treatment of Cancer (EORTC). These criteria were therefore considered acceptable. A concern was raised with respect to the use of PCR and galactomannan ELISA for the diagnostic criteria since these methods are not yet validated. The applicant, however, demonstrated that the outcome in the patients who had a final diagnostic based on these methods was similar to that seen in other patients with pulmonary aspergillosis based on positive cultures.

Patients of both sexes were included if they met criteria for *Aspergillus* diagnosis to be refractory to or intolerant of other antifungal agents.

*Refractory* was defined as demonstrating progression of infection or failure to improve after a minimum of 7 days of therapeutic doses of effective antifungal treatment (i.e. AmB, lipid formulations of AmB, itraconazole, investigational azoles with activity against *Aspergillus*).

During the scientific advice procedure, the CPMP recognised that in general, the definition of refractoriness is of major importance in studies aiming at showing activity of a salvage regimen. In addition a non-comparative design could only be acceptable if strictly refractory patients were assessed individually on a case by case basis.

*Intolerance* was defined as a doubling of creatinine or creatinine  $\geq 2.5$  mg/dl while on standard therapy, creatinine  $\geq 2.5$  mg/dl due to another pre-existing condition, or other significant intolerance to AmB or lipid formulations of AmB.

All systemic antifungal therapy was to be discontinued prior to study entry. Patients received caspofungin acetate administered intravenously (70 mg day 1 followed by 50 mg/day as a single 1 hour infusion). The duration of treatment was based on severity of the patient's underlying disease, recovery from immunosuppression and rapidity of clinical response. If possible, therapy was to be administered for a minimum of 28 days and at least 7 days after resolution of symptoms. Maximum duration of therapy was 90 days but could be extended on a case-by-case basis. The planned duration of the follow-up was 4 weeks after treatment discontinuation.

**Primary/secondary endpoints**

The primary endpoint was the proportion of patients with a favourable response at the end of treatment i.e. either complete (resolution of all attributable clinical and radiographic findings of infection) or partial (clinically significant improvement in attributable clinical and radiographic findings) clinical response. Unfavourable response was qualified as non-improvement (i.e stable disease) or deterioration of the patient condition.

Patients were also evaluated for evidence of relapse (recurrence of infection after a favourable response at end of treatment) at a follow-up visit 4 weeks after discontinuation of intravenous therapy. Microbiological outcome was evaluated as a secondary endpoint and was assessed for all patients for whom the diagnosis was based on culture.

#### Statistical analysis

This was analysed as an estimation study. Ninety five percent exact confidence intervals were calculated for the overall group proportions. A modified intention-to-treat (MITT) analysis was initially the primary analysis for evaluation of efficacy. However the analysis performed by the Independent Experts Panel, who reviewed all the cases, became the primary and conclusive efficacy analysis. This change was considered appropriate.

- Results

#### Study populations/accountability of patients

Of the 69 patients enrolled, 58 completed treatment by the data cut-off of 7-Feb-2000 (P019) and were reviewed by the Independent Expert Panel. Eleven (11) additional patients completed therapy and had data available by 19-Apr-00 (P019S). The baseline characteristics for patients enrolled in study P019 and the supplement P019S are displayed in table 2.



Table 2: Baseline characteristics

	<b>P019 (n = 58)</b>	<b>P019S (n = 11)</b>
<b>Gender</b> : male/female (n %)	35/23 (60.3 %/39.7 %)	11/0 (100.0 % 0.0 %)
<b>Race</b>		
Caucasian	55 (94.8 %)	10 (90.9 %)
Hispanic	2 (3.4 %)	1 (9.1 %)
Black	1 (1.7 %)	0 (0.0 %)
<b>Age (Years)</b>		
Mean	48.4	42.2
range	20-71	15-71
<b>Site of <i>Aspergillus</i> infection</b> (final diagnosis based on Expert Panel assessment)	N = 56 with IA	N = 9 with IA
Pulmonary, probable	17 (30.4 %)	2 (22.2 %)
Pulmonary, definite	23 (41.1 %)	4 (44.4 %)
Disseminated	10 (17.9 %)	3 (33.3 %)
Sinus	4 (7.1 %)	0 (0.0 %)
Central nervous system	1 (1.8 %)	0 (0.0 %)
Skin	0 (0.0 %)	0 (0.0 %)
Pulmonary/sinus	1 (1.8 %)	0 (0.0 %)
<b>Refractory or intolerant</b> (diagnosis based on Expert Panel assessment)	N = 56 with IA	N = 9 with IA
Refractory	46 (82.1 %)	9 (100.0 %)
Intolerant	10 (17.9 %)	0 (0.0 %)
<b>Underlying disease</b>		
Haematologic malignancies	39 (67.2 %)	7 (63.6 %)
Organ transplant	8 (13.8 %)	1 (9.1 %)
Solid tumour	2 (3.4 %)	1 (9.1 %)
Other risk factors/no clear risk factors	9 (15.5 %)**	2 (18.2 %)***
<b>Neutropenic status</b>		
Absolute neutrophil count < 500	13 (22.4 %)	3 (27.3 %)
Absolute neutrophil count ≥ 500	45 (77.6 %)	8 (72.7 %)

\* includes patients with stem cell transplants

\* includes: corticosteroids (4), no risk factor (2), methotrexate use (1), skull trauma (1), mycobacterial infection (1)

\*\*\* includes a patient with GVHD from BMT for Wiskott Aldrich Syndrome and a patient with no risk factor

The population was very heterogeneous with respect to underlying diseases, degree of immunosuppression, prior antifungal treatment and rate of *Aspergillus* progression at baseline. Of haematological malignancies (n = 39 in P019), acute myelogenous leukaemia was the most frequently reported. Twenty patients had undergone bone marrow and/or peripheral stem-cell transplantation prior to study entry. The distribution of sites of aspergillosis infection was consistent with that found in the literature. Twenty-two patients were receiving high-dose corticosteroid at study entry.

The majority of refractory patients (70 %) had received > 14 days of standard therapy and 57 % received > 21 days.

Baseline *Aspergillus* isolates showed that *A. fumigatus* was the most common pathogen identified, followed by *A. flavus*.

The mean duration of caspofungin therapy was 31.1 days ranging from 1 to 162 days. In the supplementary P019S, the mean duration of caspofungin therapy was 47 days (range 2 to 144 days).

#### *Discontinuation*

Less than half of the patients completed the study, including 4 weeks of follow-up (25/58 in P019) and the most common reason for discontinuing treatment was occurrence of clinical adverse events. As expected, mortality was high and over half of the patients died on therapy or during follow-up either due to progressive aspergillosis or to complications of underlying diseases.

## Efficacy Results

According to the Independent Expert Panel, 54 of 58 patients in P019 and 9 of 11 patients in P019S, respectively, fulfilled all the criteria of the study and were included in the efficacy analysis (n = 63). Of these 53 were considered refractory and 10 intolerant.

### *Response*

At the end of therapy, 40.7 % (22/54 patients in P019) and 44.4 % (4/9 patients in P019S) had a favourable response, as assessed by the Expert Panel, the majority being partial responses: 22 (19 in P019 + 3 in P019S) versus 4 complete responses (3 in P019 + 1 in P019S). If only patients who received > 7 days of therapy are included, 48.9 % (22 of 45 patients in P019) and 57.1 % (4 of 7 patients in P019S) had a favourable response.

During the evaluation, however, the CPMP considered that 5 patients originally classified as refractory did not fulfil the criteria for refractoriness because of inadequacy of the dose or too short duration of the prior antifungal therapy used. Therefore upon re-evaluation, 48 patients were considered refractory, including 39 from P019. The original efficacy response and the response after reclassification of the refractory patients are presented in table 3.

Table 3: Proportion of patients with a favourable overall response at discontinuation of therapy-

	FAVOURABLE RESPONSE (COMPLETE OR PARTIAL)	
	Original caspofungin Protocol 019 n/m (%)	Reclassified caspofungin Protocol 019 n/m (%)
<b>Refractory</b>		
P019	15/44 (34.1)	13/39 (33.3)
P019 + P019S	19/53 (35.8)	17/48 (35.4)
<b>Refractory or intolerant</b>		
P019	22/54 (40.7)	20/49 (40.8)
P019 + P019S	26/63 (41.3)	24/58 (41.4)

There was essentially no change in efficacy after reclassification of refractory patients.

The overall response was analysed by disease characteristics and demographics. The response rates among patients with pulmonary disease and extrapulmonary disease were 47 % (21/45) and 28 % (5/18) respectively.

As expected, response rates were lower in subgroups known to be associated with a poor prognosis such as allogenic transplants, neutropenic patients and patients with disseminated disease, although favourable responses of approximately 20 % were still reported in these subgroups. Similarly in patients on high dose corticosteroids, the overall favourable response, although decreased, still accounted for 32 %.

Two of the 14 patients who were neutropenic at study entry had a favourable response, after they recovered from their neutropenia, while none of the patients who remained neutropenic at the end of the treatment (8 of the 14 included) had a favourable response.

In a small number of patients (4), a surgical debridement or resection was performed which in most cases contributed to a favourable response to the extent that the true contribution of caspofungin in these patients became difficult to evaluate.

Among patients with extrapulmonary disease, 2 of the 8 patients who also had definite, probable or possible central nervous system (CNS) involvement had a favourable response. Although precise quantification of the amount of caspofungin present in the brain is not available, data supported that caspofungin can penetrate into the brain in the setting of inflammation. The potential efficacy in fungal infections in the CNS has therefore been reflected in the Summary of Product Characteristics.

A review of data on time to response demonstrated that time to initial response was usually not seen during the first week of caspofungin treatment but appeared between 10 to 20 days. Radiographic improvement was as expected observed later than the clinical response.

Microbiological data were limited and it was recognised that microbiological outcomes were difficult to assess in patients with IA. There was no apparent relationship between caspofungin MICs for any of the *Aspergillus* species isolated and microbiological and clinical outcome at discontinuation of treatment. The applicant committed to improve the current methods for susceptibility testing of yeasts and filamentous fungi, and to develop methods for quantitating growth of filamentous *in vitro* and in animal models that will increase the sensitivity for determination of efficacy in animal models.

#### *Follow-up*

Of the 26 patients with a favourable response at the end of caspofungin therapy, 20 were evaluated at the 4-week follow-up visit (3 patients died prior to follow-up and 3 were lost to follow-up). Only 2 patients had a relapse of IA.

Following a concern raised related to the absence of longer term clinical data, the applicant provided retrospectively information on the 20 patients who had favourable response at the end of 4-week follow-up visit. In the 3 months post therapy, only one patient died without clear evidence of the cause of death or relapse. In the 12-month follow-up, a total of 4 deaths were reported, of which there were 2 cases of relapse although it was not clear retrospectively whether they were confirmed histopathologically or microbiologically and whether they were true relapses or recurrences of the disease. These follow-up data demonstrated a sustained response to caspofungin in the majority of patients after the 4-week of follow-up period.

As this study is still ongoing, the protocol has been amended to collect longer follow-up data and include higher daily doses. The final results will be provided as part of specific obligations to be fulfilled post authorisation.

#### **Supportive studies**

- Compassionate use study (P024/025)

This is an ongoing non comparative, open, multicentre, compassionate use study aiming to evaluate the efficacy, safety and tolerability of caspofungin acetate for the treatment of IA in adults who are refractory to or intolerant of AmB or lipid formulation of AmB and for the treatment of oropharyngeal/oesophageal candidiasis and invasive candidiasis.

Three patients were diagnosed with IA, using the same diagnostic criteria as in study P019 and were treated with the same caspofungin regimen. The same Independent Expert Panel reviewed the cases.

#### *Baseline Characteristics*

One patient with aplastic anaemia and one patient with advanced AIDS had definite pulmonary aspergillosis. The third patient with no defined risk factor had disseminated aspergillosis of the lung and spine. All were refractory to standard treatment. The duration of caspofungin treatment ranged from 7 to 89 days.

#### *Overall Response*

The Expert Panel determined that 2 of the 3 patients had a favourable response. The patient with disseminated disease had a complete response. One of 2 patients who had definite pulmonary disease had a partial response. The other patient with pulmonary disease, treated only 7 days, was a failure and died from complications related to aplastic anaemia shortly after discontinuation of caspofungin therapy. Final report will be submitted as part of the specific obligations to be fulfilled post-authorisation

- Historical control *Aspergillus* study (P028/029)

The purpose of this study was to provide a historical database for comparison with the prospective *Aspergillus* salvage therapy. The CPMP, during its scientific advice, considered that this study might provide support in the assessment of the outcome of IA study. It was designed as a multicentre retrospective chart review of patients with IA treated from 1995 to 1998. From the list of potential cases identified through hospital records, patient charts were abstracted if the patient met eligibility criteria, including diagnosis of definite or probable IA and treatment with at least 7 days of therapeutic doses of standard antifungal therapy. No distinction was made between primary and salvage therapy. Data regarding the diagnosis of IA, underlying disease, doses and duration of standard antifungal therapy, and data supporting outcome after treatment were abstracted from hospital records and were reviewed by the physician-investigator at each site. Diagnostic criteria for IA and definitions of response were the same as those used in the salvage study.

Of the 229 eligible patients, 206 patients constituted the refractory or intolerant population, which is the primary comparator group for efficacy. At the end of week 1, patients were considered either refractory if they failed to improve or intolerant if they improved and their creatinine was  $\geq 2.5$  mg/dl. For further comparison, patients were divided in subgroups based on data at week 1 (refractory control population = 188; intolerant only population n = 5, 13 being excluding as it was impossible to assign them in any of the groups).

Baseline demographics were generally similar to those seen in the study P019. As in study P019, patients received AmB, lipid formulations of AmB, itraconazole or multiple agents but the distribution differed (e.g 14 % received multiple agents *versus* 33 % in P019). *A. fumigatus* was also the most common pathogen identified at baseline.

## Results

### *Overall response*

Study-site investigators determined that 35 (17 %) of 206 patients in the refractory/intolerant (R/I) population had a favourable response at the end of standard therapy (14 complete; 21 partial). The response in the refractory group was 14.4 % (27/188) and in the intolerant group 60 % (3/5 patients). The proportions of patients with a favourable response were 20 % for those with pulmonary IA and 5.6% for those with extrapulmonary IA respectively. None of the 41 patients with disseminated disease had a favourable response. Response rates were lower in subgroups of patients such as neutropenia, high-dose corticosteroids, and allogenic transplants. None of the patients who were neutropenic at the end of therapy had a favourable response. Of the 214 R/I patients (206 R/I + 8 undefined results at end of therapy), 133 (62.1 %) died during or within 72 hours after discontinuation of antifungal therapy.

### *Follow-up*

The follow-up period in this study was defined as approximately 4 weeks after the end of therapy and included the data that was available during the period from 14 to 42 days after the end of therapy. The data described were collected during this follow-up period. Of the 35 patients with a favourable response, 4 died, 9 patients were lost to follow-up and 21/22 continued to have a favourable response. One patient died in a relapse of IA.

### *Exploratory analysis: P019/P019S and historical control.*

A comparison was performed between historical control study and the salvage therapy study. The baseline characteristics of the patients in both studies were similar. As the refractory definition in the historical control study was broader than in study P019, patients who were truly refractory to standard antifungal therapy in study P019 were compared to a group of patients who were not truly refractory and would therefore be expected to have a better outcome. Results are displayed in Table 4.

Across all subgroups the efficacy of caspofungin in the salvage study was consistently greater than the efficacy of standard therapy in the historical control study.

Table 4: Comparison between the proportion of patients with a favourable overall response at discontinuation of therapy in Protocol P019 (after reclassification of refractory)/P019S and historical control study

	Favourable response (complete or partial) n/m (%)
<b>Refractory</b>	
P019	13/39 (33.3)
P019 + P019S	17/48 (35.4)
Historical control	27/188 (14.4)
<b>Refractory or intolerant</b>	
P019	20/49 (40.8)
P019 + P019S	24/58 (41.4)
Historical control	35/206 (17 %)

A more formal quantitative comparison of the results of Protocols 019 and 028/029 was conducted using stepwise logistic regression. For all the different models considered, adjusting for the distribution of well recognised risk factors (disseminated disease, neutropenia, bone marrow transplantation and high dose corticosteroids at week 1) the analysis demonstrated that caspofungin was statistically significantly better than standard antifungal therapy in the treatment of patients with IA who were refractory to or intolerant of prior therapy. These results provided some support to the efficacy of caspofungin.

An additional comparison was made including only patients in historical control study who received more than 14 days of prior therapy instead of 7 days. In the analysis, 34 of 140 (24.3 %) refractory or intolerant patients had a favourable response to standard antifungal therapy while when considering refractory patients only 26 of 124 (21 %) had a favourable response. The responses in the caspofungin group were higher than the responses in the historical group (41.1 % and 35.4 % respectively).

- Phase II studies in *Candida* infections (P003, P004, P007)

Three studies in *Candida* infections were conducted in patients with oesophageal and/or oropharyngeal candidiasis and were only supportive since no indication was claimed. Their objectives were to assess the safety and efficacy of caspofungin (as compared to AmB), and to determine the optimal dose of caspofungin to treat these patients, and afterwards to use in patients with deep-seated tissue infections due to *Aspergillus* (see above Dose response Studies).

As expected, the majority of infections were due to *C. albicans*. The percentage of patients with a favourable microbiological response was similar to the percentage with a favourable clinical response and did not appear to depend on the specific pathogens isolated or the MIC at baseline. The number of infections due to non-albicans *Candida* spp. was however too small to draw conclusions. In the cases with microbiological persistence, there was little change in MIC ( $\leq$  2-fold increase) for caspofungin.

### **Clinical studies in special populations**

Efficacy studies of caspofungin did not target any special populations. The study population in the *Aspergillus* salvage study was very heterogeneous including patients with severe underlying diseases and immune dysfunction, whereas the study population in the *Candida* trials mainly consisted of patients with advanced HIV disease.

The efficacy of caspofungin in the treatment of IA has not yet been evaluated in children and adolescents and therefore is not recommended for use in patients under 18 years of age. A paediatric programme is under development and data will be submitted as part of follow-up measures to be fulfilled post-authorisation.

### **Clinical safety**

The safety data supporting this application derived from caspofungin clinical pharmacology studies and clinical studies in patients with *Aspergillus* or *Candida* infections. This included safety data from the phase III randomised comparative trial of caspofungin *versus* fluconazole in oesophageal

candidiasis (P020). In addition blinded data on serious adverse events from ongoing studies P014 (invasive candidiasis) and P026 (empirical therapy) were provided. Although the indication sought is for the treatment of invasive aspergillosis, studies in patients with *Candida* infections provided important supportive data since patients had less severe diseases than the patients with *Aspergillus* infections and fewer confounding acute background illnesses. Furthermore, these were comparative studies and a higher dose of caspofungin was used (70 mg/day for up to 14 days).

- Patient exposure

In total, safety data included 843 patients enrolled in clinical pharmacology and clinical studies. Overall 623 patients received caspofungin acetate; 478 (553 if the subjects who were enrolled in the Phase I caspofungin interaction studies are included) received caspofungin at doses  $\geq$  50 mg, and 220 received placebo/comparator agents. Twelve phase I studies enrolled 312 subjects, of whom 274 received caspofungin; 191 received caspofungin alone and 83 received caspofungin with other agents, either as single dose or as multiple doses. The safety data of caspofungin from the clinical studies included both *Candida* (n = 277) and *Aspergillus* (n = 72) infections. In the *Candida* trials, 50 mg was the most commonly administered dose for a mean duration of therapy of 16 days. The total duration of exposure to caspofungin 50 mg in patients with IA was longer, with a mean duration of therapy of 33.7 days (ranging from 1 to 162 days). The number of patients who received caspofungin treatment for at least 28 days was however limited (33 in study P019, 2 in the compassionate use study and 1 in the pharmacokinetic study in *Candida* oesophagitis).

- Adverse events and serious adverse events/deaths

There was no death in the caspofungin clinical pharmacology studies. In the *Candida* clinical trials deaths occurred in 15/263 patients receiving caspofungin and in 13/182 receiving AmB or fluconazole. In the *Aspergillus* study (P019/P019S) 38/69 (55 %) patients died (162/206 (78.6 %) in the historical control study). Because of the complexity of the patient's clinical courses, attributable mortality in the caspofungin *Aspergillus* study was not specifically determined. The primary efficacy endpoint was the proportion of patients with a favourable response but information regarding death during treatment and follow up was collected, and investigators reported the cause of death for patients based on their clinical judgement. The information regarding investigator defined cause of death combined with the available autopsy data was used to define a conservative estimate that 24 of the 38 deaths were due to IA or its consequences.

The majority of serious adverse events (SAEs) occurring during the clinical trials were not considered to be related to caspofungin. In the *Candida* trials there were no SAEs reported in the caspofungin groups versus 4.5 % and 1.1% in the AmB and in the fluconazole groups, respectively. The SAE described (pulmonary infiltrates) was the only clinical SAE considered related to caspofungin that was reported in the patients with IA in the caspofungin *Aspergillus* study. There was also a laboratory SAE of hypercalcemia that was considered caspofungin-related by the investigator.

The most frequently reported clinical adverse events related to caspofungin in the *Candida* studies were consistent with those reported overall and included fever, phlebitis/thrombophlebitis and/or infused vein complication, and to a lesser extent headache and nausea. Most reactions were mild, non-serious and of short duration, and very few of them led to discontinuation of therapy. The overall incidence of clinical and laboratory adverse events was generally comparable to that observed with fluconazole and was better than that observed with AmB.

In the P019 study, the adverse experience profile was generally similar to that observed in the controlled clinical studies for *Candida* infections, but patients in this study were more severely ill and had several background conditions, making a safety evaluation difficult. There are, however, no comparative data with AmB or the less toxic lipid formulations of AmB or itraconazole in these patients. Moreover, study P019 was performed in a limited number of patients of which very few received extended therapy (only 33 patients received > 28 days of therapy, including 19 for 29 to 60 days, 8 for > 60 days, and only 4 for > 90 days). Therefore, it is not possible to draw conclusions on the long term safety profile of caspofungin.

Caspofungin caused irritation at injection sites in preclinical repeat dose toxicity studies, especially when extravasation of dosing solution occurred. Pre- and post-dose flushing with saline markedly reduced these reactions. In the controlled *Candida* studies, local reactogenicity, in terms of caspofungin related phlebitis and infused vein reactions (30/164, 18.3% in the 50 mg group and 10/65, 15.4% in the 70 mg group) were similar to AmB (20/89, 22.5%) and fluconazole (16/93, 17.2%). Most injection site reactions were mild/moderate and did not result in treatment discontinuation. Although no special precautions are currently warranted, serious local reactions will be closely monitored during the post-marketing phase.

Rash occurred in 27 (8 %) of the approximately 340 patients in the phase II/III who received caspofungin and mostly in HIV patients with oesophageal/oropharyngeal candidiasis. Most patients experiencing rash had underlying conditions and concomitant medications, therefore a causal role of caspofungin is uncertain. Most rashes seemed mild and only 2 patients had to discontinue treatment. Although results from the interaction study suggested a higher incidence of rash when caspofungin is co-administered with itraconazole, there was no apparent relationship between the administration of itraconazole and rash in study P019.

Based on preclinical observations, reactions due to histamine release were carefully monitored in human clinical trials. In the first phase I multiple dose study (study P002), local erythema and pruritus were frequently reported. To confirm whether or not these reactions were related to local histamine release, a small study was performed to evaluate any potential benefit of pre-treatment with antihistamine. There was no evidence that antihistamine treatment would be beneficial and therefore no pre-treatment was recommended in Phase II/III studies. In these studies, there were reports of symptoms such as rash, facial swelling, erythema, pruritus and hypotension but it was not clear if these were histamine mediated. In the compassionate use study, however, one patient with IA experienced stridor, dyspnea and worsening rash during the initial infusion of caspofungin, which are consistent with acute systemic histamine mediated reaction. These symptoms resolved with discontinuation of caspofungin and treatment with corticosteroid and diphenhydramine. Therefore, in order to clarify the potential risk associated with caspofungin, the applicant committed to closely monitor acute systemic histamine-like reactions during the post-marketing surveillance.

Hypotension and arrhythmias occurred in patients with IA, typically in the setting of sepsis or respiratory failure. Respiratory adverse events were reported in patients with pulmonary aspergillosis (respiratory distress/failure) and in patient in the *Candida* oesophagitis studies (infectious bronchitis/pneumonia). None of these events seemed however to be related to caspofungin.

As mentioned in the Pharmacotoxicological part of this document, there was evidence of low levels of irreversible binding of caspofungin degradates to plasma proteins. Preclinical studies did not suggest any pattern of safety reactions due to this effect. No specific adverse reactions were identified in the clinical studies that could be related to covalent binding. However, the applicant committed to carefully monitor during the post-marketing phase for any unusual serious events that could be related to irreversible binding of caspofungin degradates.

A review of the patients receiving more than 28 days of caspofungin treatment showed that there were no specific safety problems related to duration of treatment, but only few patients received extended therapy, and thus the long term safety data are currently insufficient.

- Laboratory findings

The most common caspofungin-related laboratory abnormalities reported were increased transaminases (AST and ALT). The incidence varied among healthy volunteers (0-6 %), patients with candidiasis (11-24 %) and aspergillosis (14 %). In the latter study, alkaline phosphatase was also increased in 21 % of patients. Most increases of ALT/AST were < 5-fold ULN and did not limit therapy. No apparent dose-effect relationship was demonstrated. The mechanism of transaminase elevations is currently unknown. Elevations in ALP were common in patients in study P019, but were

not associated with elevations in other liver enzymes. Underlying conditions and concomitant medications contributed to the ALP elevations.

In addition, decreased haemoglobin and decreased haematocrit were reported. Serum creatinine elevations occurred in only 1 patient receiving caspofungin versus 28% of patients receiving AmB.

- Safety in special populations

No adverse effects on liver function tests were observed in patients with hepatic insufficiency receiving caspofungin.

The safety of caspofungin in children and adolescents has not yet been established.

## **5. Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

Caspofungin is a complex molecule isolated by chemical modification of a substance obtained by fermentation. The problems of poor solid-state stability of the active substance have been overcome, by rational formulation in a stabilising matrix, which allows a sterile pyrogen-free lyophilisate, suitable for parenteral use, to be obtained. The reconstitution of this powder has been studied and selected diluents have been defined, in order to allow a stable solution at 'room temperature' to give flexibility and ease of handling prior to and during administration.

The quality of Caspofungin MSD was considered acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics.

### **Preclinical pharmacology and toxicology**

In summary, the primary pharmacodynamic studies provided adequate evidence that caspofungin, which differs from current antifungal agents by its mode of action (glucan synthesis inhibitor), has an *in vitro* and *in vivo* activity against *Aspergillus*, compatible with a clinical use in invasive aspergillosis. This was mostly shown in *A. fumigatus*, but the applicant undertook to further investigate the activity of caspofungin against other *Aspergillus* species. Although the nature of the activity of caspofungin against *Aspergillus* (fungicidal/fungistatic) was extensively studied, some uncertainties still remain. In addition, based on the results, it was difficult to conclude on the synergistic activity between caspofungin and AmB or fluconazole, however the importance of further investigating these combinations in animal models was highlighted.

The pharmacokinetics profile of caspofungin was adequately defined, although additional data, such as metabolite data in mouse and rabbit will be submitted post-authorisation. Caspofungin distributed widely, was highly protein bound, eliminated slowly and excreted mainly by urinary route.

Overall, the toxicology programme revealed that the primary toxicological targets were the liver in monkeys, effects related to histamine release in rats and injection sites in both species. Based on the results from developmental toxicity studies, a potential for reproduction toxicity of caspofungin cannot be excluded. Caspofungin crosses the placental barrier and is excreted in milk. Caspofungin was not genotoxic and the absence of carcinogenicity studies was adequately justified. The NOELs identified in repeated dose toxicity studies and reproduction toxicity studies corresponded to doses providing a low margin of exposure in relation to expected clinical exposure. The Summary of Product Characteristics adequately reflects the toxicological data and includes relevant warnings on the potential risk in pregnancy and breast-feeding.



## **Efficacy**

The pharmacokinetic profile of caspofungin was generally well documented and was considered sufficient for the indication sought. Although data in patients with IA were scarce, they suggested that the pharmacokinetic profile in this population is similar to the one obtained in patients with candidiasis. Adequate dosage recommendations were defined for patients with hepatic and renal impairment. The importance to further evaluate some combination regimens, particularly the association of caspofungin with AmB or itraconazole, was highlighted as these compounds are expected to be used in close association.

The concern was raised that proposed dose of caspofungin (70 mg loading dose followed by 50 mg once daily) would not ensure adequate exposure in all patients considering the great inter-patient variability in pharmacokinetic parameters, the influence of body weight and the absence of a defined relationship between PK/PD.

Overall the efficacy of caspofungin in adult patients with IA refractory or intolerant to AmB, lipid formulation of AmB or itraconazole, was demonstrated mainly in one open-label, non-comparative study enrolling a limited number of patients. The clinical benefit of caspofungin was demonstrated: 35.4 % (17/48) of refractory patients receiving at least one dose of caspofungin had a favourable response and 41.4 % (24/58) of refractory or intolerant patients had a favourable response. A major concern was the limited period of follow-up (only 4 weeks), especially considering the new mechanism of action of this agent. The maintaining of the significant benefit of caspofungin compared to standard therapy following adjustment of the number of truly refractory patients was questioned.

## **Safety**

Given the life-threatening and poor prognosis of invasive aspergillosis, the safety database, although limited, was considered acceptable. Overall the data did not reveal any major safety concerns. The most common adverse events were fever, infused-vein complications, nausea, vomiting and flushing. In the IA study, the safety profile was generally similar to that observed in the controlled clinical studies for *Candida* infections, but patients in this study were more severely ill and had several background conditions, making a safety evaluation difficult. No comparative data with AmB or the less toxic lipid formulations of AmB or itraconazole are available in these patients. The long term safety is currently unknown since only limited data on treatment duration longer than 2 weeks. It seems however that caspofungin continues to be well tolerated with longer courses of therapy (68 patients received from 15 to 60 days and 12 patients received from 61 to 162 days of treatment). The applicant undertook to perform a close post-monitoring surveillance, with particular attention to some specific issues such as histamine-mediated reactions, hepatotoxic reactions and allergic reactions related to long-lived caspofungin degradates.

## **Benefit/risk assessment**

Invasive aspergillosis is a rare, very serious disease with, if untreated, a mortality of 100 %. Despite the availability of treatments such as AmB, there is a need for safer and more efficacious compounds to treat this life-threatening disease. Caspofungin appeared to be beneficial as salvage therapy in the treatment of invasive aspergillosis, since efficacy was demonstrated in truly refractory patients with no other therapeutic options.

During an oral explanation before the CPMP and subsequent written responses, the applicant addressed CPMP concerns over the dosage recommendations, the follow-up after treatment stop, the fungistatic/fungicidal activity of caspofungin and the co-administration of caspofungin and cyclosporin A.

Based on pharmacokinetic considerations, it was agreed to increase the maintenance dose from 50 mg to 70 mg daily in patients weighing more than 80 kg, as described in the Clinical part of this document. Additional pharmacokinetic and efficacy data will be submitted as part of specific obligations to be fulfilled post-authorisation to support the recommendation for higher doses of caspofungin.

As further discussed in the Clinical part of this document, it was demonstrated that there was no difference in efficacy following adjustment of the number of truly refractory patients in study P019 and that the benefit of caspofungin when compared to standard therapy in the Historical Control Study remained unchanged. To further substantiate the clinical benefit of caspofungin therapy, the applicant undertook to submit final results from studies P019 and P024/025 as part of specific obligations to be fulfilled

With respect to longer follow-up data after treatment stop, the applicant retrospectively presented data for all patients with a favourable response at the 4-week follow-up visit. Results, which are further presented in the Clinical part of this document, demonstrated a sustained response to caspofungin therapy. To further substantiate the long term clinical benefit of caspofungin therapy, the applicant undertook to submit additional data at 3 months follow-up from study P019 and all future studies in this indication as part of specific obligations to be fulfilled and to evaluate the use of secondary suppressive antifungal therapy at the end of caspofungin treatment.

Although the nature of the activity of caspofungin was extensively investigated, caspofungin is neither fungicidal nor fungistatic by classical definition but is fungicidal to *Aspergillus* hyphae at its tips and branch points where cell growth and division occur. The applicant undertook to further clarify this issue during the post-authorisation phase.

With respect to the combination with cyclosporin A, there are currently not enough data to recommend any dose adjustment but studies are ongoing. In the meantime adequate warning concerning the monitoring of liver tests has been included in the Summary of Product Characteristics. In addition the applicant undertook to evaluate combination regimens with caspofungin, results of which will be submitted as part of specific obligations to be fulfilled post-authorisation.

Finally, the applicant undertook to provide further data on other outstanding issues in relation to pharmaceutical, toxicological and clinical aspects of the dossier, as part of follow-up measures to be fulfilled post-authorisation.

### **Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of caspofungin in the treatment of invasive aspergillosis in adult patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole was favourable.

The divergent opinion was that the benefit-risk ratio could not be defined because of, the number of patients in which the efficacy and safety of Caspofungin MSD was evaluated was too small; the above mentioned evaluations were not comparative but based on historical controls and therefore could be heavily biased; and a fully reliable recommendation on optimal dose and schedule of Caspofungin MSD was lacking.

Considering the small number of patients evaluated with limited follow-up and safety data, and waiting additional clinical data in this indication, the CPMP recommended the granting of the marketing authorisation for Caspofungin MSD (50 mg powder for solution for infusion and 50 mg and 70 mg powder for concentrate for solution for infusion) under exceptional circumstances for the following indication:

“Treatment of invasive aspergillosis in adult 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”.