ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 50 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg caspofungin(as acetate).

Each 50mg vial contains 35.7 mg of sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white compact, lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive candidiasis in adult patients.
- 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.
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropaenic adult patients.

4.2 Posology and method of administration

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

After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour. Do not mix or co-infuse CANCIDAS with other medicines, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products. DO NOT USE DILUENTS CONTAINING GLUCOSE, as CANCIDAS is not stable in diluents containing glucose. For reconstitution directions see section 6.6.

Both 70 mg and 50 mg vials are available.

A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, CANCIDAS 70 mg daily is recommended (see section 5.2). Doses higher than 70 mg daily have not been adequately studied.

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

Duration of treatment of invasive candidiasis should be based upon the patient's clinical and microbiological response. After signs and symptoms of invasive candidiasis have improved and

cultures have become negative, a switch to oral antifungal therapy may be considered. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

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

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

No dosage adjustment is necessary based on gender, race, or renal impairment (see section 5.2).

For mild hepatic insufficiency (Child-Pugh score 5 to 6), no dosage adjustment is needed. For patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35 mg daily is recommended. An initial 70 mg loading dose should be administered on Day-1. There is no clinical experience with severe hepatic insufficiency (Child-Pugh score greater than 9) (see section 4.4).

The experience in children is limited.

Limited data suggest that an increase in the daily dose of CANCIDAS to 70 mg, following the 70 mg loading dose, should be considered when co-administering CANCIDAS with certain inducers of metabolic enzymes (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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

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

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

The safety information on treatment durations longer than 4 weeks is limited.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

4.6 Pregnancy and lactation

For CANCIDAS, no clinical data on exposed pregnancies are available. Caspofungin should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of caspofungin in pregnant women. Developmental studies in animals have shown adverse effects (see section 5.3). Caspofungin has been shown to cross the placental barrier in animal studies. The potential risk to the human foetus is unknown.

Caspofungin is excreted in milk of lactating animals. It is not known whether it is excreted in human milk. Women receiving caspofungin should not breast-feed.

4.7 Effects on ability to drive and use machines

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

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4.8 Undesirable effects

In clinical studies, 1440 individuals received single or multiple doses of CANCIDAS: 564 febrile neutropaenic patients (empirical therapy study), 125 patients with invasive candidiasis, 72 patients with invasive aspergillosis, 285 patients with localised *Candida* infections, and 394 individuals enrolled in Phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation (including 39 allogeneic transplantations). In the studies involving patients with documented *Candida* infections, the majority of the patients with invasive *Candida* infections had serious underlying medical conditions (e.g., haematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the non-comparative *Aspergillus* study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications.

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

Reported clinical and laboratory abnormalities among all patients treated with CANCIDAS (total 989) were typically mild and rarely led to discontinuation.

The following adverse reactions were reported:

[Very common (≥1/10), Common (≥1/100, < 1/10)]

Blood and lymphatic system disorders:
Common: anaemia

Nervous system disorders:
Common: headache

Cardiac disorders:
Common: tachycardia

Vascular disorders:
Common: phlebitis/thrombophlebitis, flushing

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea

Gastrointestinal disorders:
Common: abdominal pain, nausea, diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Common: rash, pruritus, sweating

General disorders and administration site conditions:
Very common: fever
Common: pain, chills, infused-vein complications

Investigations:
Common: elevated liver values (AST, ALT, alkaline phosphatase, direct and total bilirubin), increased serum creatinine, decreased haemoglobin, decreased haematocrit, blood potassium decreased, hypomagnesaemia, low albumin, decreased white blood cells, increased eosinophils, platelet count decreased, decreased neutrophils, increased urinary red blood cells, increased partial thromboplastin time, decreased total serum protein, increased urinary protein, increased prothrombin time, blood

sodium decreased, increased urinary white blood cells and low calcium. High calcium has been reported as uncommon (≥1/1000, <1/100).

Possible histamine-mediated symptoms have been reported including reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Anaphylaxis has been reported during administration of caspofungin.

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

Post-Marketing experience:
The following post-marketing adverse events have been reported:

Hepatobiliary disorders:
Hepatic dysfunction

General disorders and administration site conditions:
Swelling and peripheral oedema

Investigations:
Hypercalcaemia

4.9 Overdose

Inadvertent administration of up to 140 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse experiences. Caspofungin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Caspofungin has *in vitro* activity against *Aspergillus* species (*Aspergillus fumigatus* [N = 75], *Aspergillus flavus* [N = 111], *Aspergillus niger* [N = 31], *Aspergillus nidulans* [N = 8], *Aspergillus terreus* [N = 52], and *Aspergillus candidus* [N = 3]). Caspofungin also has *in vitro* activity against *Candida* species (*Candida albicans* [N = 1032], *Candida dubliniensis* [N = 100], *Candida glabrata* [N = 151], *Candida guilliermondii* [N = 67], *Candida kefyr* [N = 62], *Candida krusei* [N = 147], *Candida lipolytica* [N = 20], *Candida lusitaniae* [N = 80], *Candida parapsilosis* [N = 215], *Candida rugosa* [N = 1], and *Candida tropicalis* [N = 258]), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-flucytosine. Susceptibility testing was performed according to a modification of both the National Committee for Clinical Laboratory Standards (NCCLS) method M38-A (for *Aspergillus* species) and method M27-A (for *Candida* species). Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment. However, standardised techniques for susceptibility testing for antifungal agents, including beta (1,3)-D-glucan synthesis inhibitors, have not been established. MIC values for caspofungin should not be used to predict clinical outcome, since a

correlation between MIC values and clinical outcome has not been established. Development of *in vitro* resistance to caspofungin by *Aspergillus* species has not been identified. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has not been observed. The incidence of resistance to caspofungin by various clinical isolates of *Candida* and *Aspergillus* is unknown.

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

Invasive Aspergillosis: Sixty-nine adult patients (age 18-80) with invasive aspergillosis were enrolled in an open-label, non-comparative study to evaluate the safety, tolerability, and efficacy of caspofungin. Patients had to be either refractory to (disease progression or failure to improve with other antifungal therapies given for at least 7 days) (84 % of the enrolled patients) or intolerant of (16 % of enrolled patients) other standard antifungal therapies. Most patients had underlying conditions (haematologic malignancy [N = 24], allogeneic bone marrow transplant or stem cell transplant [N = 18], organ transplant [N = 8], solid tumour [N = 3], or other conditions [N = 10]). Stringent definitions, modelled after the Mycoses Study Group Criteria, were used for diagnosis of invasive aspergillosis and for response to therapy (favourable response required clinically significant improvement in radiographs as well as in signs and symptoms). The mean duration of therapy was 33.7 days, with a range of 1 to 162 days. An independent expert panel determined that 41 % (26/63) of patients receiving at least one dose of caspofungin had a favourable response. For those patients who received more than 7 days of therapy with caspofungin, 50 % (26/52) had a favourable response. The favourable response rates for patients who were either refractory to or intolerant of previous therapies were 36 % (19/53) and 70 % (7/10), respectively. Although the doses of prior antifungal therapies in 5 patients enrolled as refractory were lower than those often administered for invasive aspergillosis, the favourable response rate during therapy with caspofungin was similar in these patients to that seen in the remaining refractory patients (2/5 versus 17/48, respectively). The response rates among patients with pulmonary disease and extrapulmonary disease were 47 % (21/45) and 28 % (5/18), respectively. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favourable response.

Empirical Therapy in Febrile, Neutropaenic Adult Patients: A total of 1111 patients with persistent fever and neutropaenia were enrolled in a clinical study and treated with either caspofungin 50 mg once daily following a 70 mg loading dose or liposomal amphotericin B 3.0 mg/kg/day. Eligible patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation, and presented with neutropaenia (<500 cells/mm^3 for 96 hours) and fever (>38.0°C) not responding to ≥96 hours of parenteral antibacterial therapy. Patients were to be treated until up to 72 hours after resolution of neutropaenia, with a maximum duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated after 5 days of therapy, the dosage of study drug could be increased to 70 mg/day of caspofungin (13.3 % of patients treated) or to

5.0 mg/kg/day of liposomal amphotericin B (14.3 % of patients treated).There were 1095 patients included in the primary Modified Intention-To-Treat (MITT) efficacy analysis of overall favourable response; caspofungin (33.9 %) was as effective as liposomal amphotericin B (33.7 %) [% difference 0.2 (95.2 % CI –5.6, 6.0)]. An overall favourable response required meeting each of 5 criteria: (1) successful treatment of any baseline fungal infection (caspofungin 51.9 % [14/27], liposomal amphotericin B 25.9 % [7/27]), (2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment (caspofungin 94.8 % [527/556], liposomal amphotericin B 95.5 % [515/539]), (3) survival for 7 days after completion of study therapy (caspofungin 92.6 % [515/556], liposomal amphotericin B 89.2 % [481/539]), (4) no discontinuation from the study drug because of drug-related toxicity or lack of efficacy (caspofungin 89.7 % [499/556], liposomal amphotericin B 85.5 % [461/539]), and (5) resolution of fever during the period of neutropaenia (caspofungin 41.2 % [229/556], liposomal amphotericin B 41.4 % [223/539]). Response rates to caspofungin and liposomal amphotericin B for baseline infections caused by *Aspergillus* species were, respectively, 41.7 % (5/12) and 8.3 % (1/12), and by *Candida* species were 66.7 % (8/12) and 41.7 % (5/12). Patients in the caspofungin group experienced breakthrough infections due to the following uncommon yeasts and moulds: *Trichosporon* species (1), *Fusarium* species (1), *Mucor* species (1), and *Rhizopus* species (1).

5.2 Pharmacokinetic properties

Distribution

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

Metabolism

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

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

Elimination and excretion

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

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

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

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Mannitol
Glacial acetic acid

Sodium hydroxide (to adjust the pH)

6.2 Incompatibilities

Do not mix with diluents containing glucose, as CANCIDAS is not stable in diluents containing glucose. Do not mix or co-infuse CANCIDAS with other medicinal products, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products.

6.3 Shelf life

2 years

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

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

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

6.4 Special precautions for storage

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

For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

10 ml Type I glass vials with a grey butyl stopper and a plastic cap with a red aluminium band for single use only.
Supplied in packs of 1 vial.

6.6 Special precautions for disposal

No special requirements.

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

Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injections. The concentrations of the reconstituted vials will be: 5 mg/ml.

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

Step 2 Addition of Reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or has precipitated. This infusion solution must be used within 24 hours if stored at or below 25°C, or within 48 hours if stored refrigerated at 2 to 8°C. Chemical and physical in-use stability of the diluted solution in sterile lactated Ringer's solution and sodium chloride solution 9 mg/ml (0.9 %), 4.5 mg/ml (0.45 %), and 2.25 mg/ml (0.225 %) for infusion has been demonstrated for 24 hours at 25°C and for 48 hours at 2 to 8°C. From a microbiological point of view, the solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

PREPARATION OF THE SOLUTION FOR INFUSION

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
50 mg	10 ml	0.19 mg/ml	-
50 mg at reduced volume	10 ml	-	0.45 mg/ml
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 ml	0.14 mg/ml	-
35 mg for moderate hepatic insufficiency (from one 50 mg vial) at reduced volume	7 ml	-	0.33 mg/ml

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of last renewal

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 50 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with transfer set contains 50 mg caspofungin (as acetate).

Each 50 mg vial contains 35.7 mg of sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white compact, lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive candidiasis in adult patients.
- 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.
- Empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus)* in febrile, neutropaenic adult patients.

4.2 Posology and method of administration

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

After reconstitution, the solution should be administered by slow intravenous infusion over approximately 1 hour. Do not mix or co-infuse CANCIDAS with other medicines, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products. DO NOT USE DILUENTS CONTAINING GLUCOSE, as CANCIDAS is not stable in diluents containing glucose. For reconstitution directions see section 6.6.

Both 70 mg and 50 mg vials are available.

A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, CANCIDAS 70 mg daily is recommended (see section 5.2).
Doses higher than 70 mg daily have not been adequately studied.

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

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

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

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

No dosage adjustment is necessary based on gender, race, or renal impairment (see section 5.2).

For mild hepatic insufficiency (Child-Pugh score 5 to 6), no dosage adjustment is needed. For patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35 mg daily is recommended. An initial 70 mg loading dose should be administered on Day-1. There is no clinical experience with severe hepatic insufficiency (Child-Pugh score greater than 9) (see section 4.4).

The experience in children is limited.

Limited data suggest that an increase in the daily dose of CANCIDAS to 70 mg, following the 70 mg loading dose, should be considered when co-administering CANCIDAS with certain inducers of metabolic enzymes (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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

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

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

The safety information on treatment durations longer than 4 weeks is limited.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

4.6 Pregnancy and lactation

For CANCIDAS, no clinical data on exposed pregnancies are available. Caspofungin should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of caspofungin in pregnant women. Developmental studies in animals have shown adverse effects (see section 5.3). Caspofungin has been shown to cross the placental barrier in animal studies. The potential risk to the human foetus is unknown.

Caspofungin is excreted in milk of lactating animals. It is not known whether it is excreted in human milk. Women receiving caspofungin should not breast-feed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In clinical studies, 1440 individuals received single or multiple doses of CANCIDAS: 564 febrile neutropaenic patients (empirical therapy study), 125 patients with invasive candidiasis, 72 patients with invasive aspergillosis, 285 patients with localised *Candida* infections, and 394 individuals enrolled in Phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation (including 39 allogeneic transplantations). In the studies involving patients with documented *Candida* infections, the majority of the patients with invasive *Candida* infections had serious underlying medical conditions (e.g., haematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the non-comparative *Aspergillus* study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications.

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

Reported clinical and laboratory abnormalities among all patients treated with CANCIDAS (total 989) were typically mild and rarely led to discontinuation.

The following adverse reactions were reported:

[Very common (≥1/10), Common (≥1/100, < 1/10)]

Blood and lymphatic system disorders:
Common: anaemia

Nervous system disorders:
Common: headache

Cardiac disorders:
Common: tachycardia

Vascular disorders:
Common: phlebitis/thrombophlebitis, flushing

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea

Gastrointestinal disorders:
Common: abdominal pain, nausea, diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Common: rash, pruritus, sweating

General disorders and administration site conditions:
Very common: fever
Common: pain, chills, infused-vein complications

Investigations:
Common: elevated liver values (AST, ALT, alkaline phosphatase, direct and total bilirubin), increased serum creatinine, decreased haemoglobin, decreased haematocrit, blood potassium decreased, hypomagnesaemia, low albumin, decreased white blood cells, increased eosinophils, platelet count decreased, decreased neutrophils, increased urinary red blood cells, increased partial thromboplastin time, decreased total serum protein, increased urinary protein, increased prothrombin time, blood

sodium decreased, increased urinary white blood cells and low calcium. High calcium has been reported as uncommon (≥1/1000, <1/100).

Possible histamine-mediated symptoms have been reported including reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Anaphylaxis has been reported during administration of caspofungin.

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

Post-Marketing experience:
The following post-marketing adverse events have been reported:

Hepatobiliary disorders:
Hepatic dysfunction

General disorders and administration site conditions:
Swelling and peripheral oedema

Investigations:
Hypercalcaemia

4.9 Overdose

Inadvertent administration of up to 140 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse experiences. Caspofungin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Caspofungin has *in vitro* activity against *Aspergillus* species (*Aspergillus fumigatus* [N = 75], *Aspergillus flavus* [N = 111], *Aspergillus niger* [N = 31], *Aspergillus nidulans* [N = 8], *Aspergillus terreus*[N = 52], and *Aspergillus candidus* [N = 3]). Caspofungin also has *in vitro* activity against *Candida* species (*Candida albicans* [N = 1032], *Candida dubliniensis* [N = 100], *Candida glabrata* [N = 151], *Candida guilliermondii* [N = 67], *Candida kefyr* [N = 62], *Candida krusei* [N = 147], *Candida lipolytica* [N = 20], *Candida lusitaniae* [N = 80], *Candida parapsilosis* [N = 215], *Candida rugosa* [N = 1], and *Candida tropicalis* [N = 258]), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-flucytosine. Susceptibility testing was performed according to a modification of both the National Committee for Clinical Laboratory Standards (NCCLS) method M38-A (for *Aspergillus* species) and method M27-A (for *Candida* species). Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment. However, standardised techniques for susceptibility testing for antifungal agents, including beta (1,3)-D-glucan synthesis inhibitors, have not been established. MIC values for caspofungin should not be used to predict clinical outcome, since a

correlation between MIC values and clinical outcome has not been established. Development of *in vitro* resistance to caspofungin by *Aspergillus* species has not been identified. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has not been observed. The incidence of resistance to caspofungin by various clinical isolates of *Candida* and *Aspergillus* is unknown.

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

Invasive Aspergillosis: Sixty-nine adult patients (age 18-80) with invasive aspergillosis were enrolled in an open-label, non-comparative study to evaluate the safety, tolerability, and efficacy of caspofungin. Patients had to be either refractory to (disease progression or failure to improve with other antifungal therapies given for at least 7 days) (84 % of the enrolled patients) or intolerant of (16 % of enrolled patients) other standard antifungal therapies. Most patients had underlying conditions (haematologic malignancy [N = 24], allogeneic bone marrow transplant or stem cell transplant [N = 18], organ transplant [N = 8], solid tumour [N = 3], or other conditions [N = 10]). Stringent definitions, modelled after the Mycoses Study Group Criteria, were used for diagnosis of invasive aspergillosis and for response to therapy (favourable response required clinically significant improvement in radiographs as well as in signs and symptoms). The mean duration of therapy was 33.7 days, with a range of 1 to 162 days. An independent expert panel determined that 41 % (26/63) of patients receiving at least one dose of caspofungin had a favourable response. For those patients who received more than 7 days of therapy with caspofungin, 50 % (26/52) had a favourable response. The favourable response rates for patients who were either refractory to or intolerant of previous therapies were 36 % (19/53) and 70 % (7/10), respectively. Although the doses of prior antifungal therapies in 5 patients enrolled as refractory were lower than those often administered for invasive aspergillosis, the favourable response rate during therapy with caspofungin was similar in these patients to that seen in the remaining refractory patients (2/5 versus 17/48, respectively). The response rates among patients with pulmonary disease and extrapulmonary disease were 47 % (21/45) and 28 % (5/18), respectively. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favourable response.

Empirical Therapy in Febrile, Neutropaenic Adult Patients: A total of 1111 patients with persistent fever and neutropaenia were enrolled in a clinical study and treated with either caspofungin 50 mg once daily following a 70 mg loading dose or liposomal amphotericin B 3.0 mg/kg/day. Eligible patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation, and presented with neutropaenia (<500 cells/mm^3 for 96 hours) and fever (>38.0°C) not responding to ≥96 hours of parenteral antibacterial therapy. Patients were to be treated until up to 72 hours after resolution of neutropaenia, with a maximum duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated after 5 days of therapy, the dosage of study drug could be increased to 70 mg/day of caspofungin (13.3 % of patients treated) or to

5.0 mg/kg/day of liposomal amphotericin B (14.3 % of patients treated).There were 1095 patients included in the primary Modified Intention-To-Treat (MITT) efficacy analysis of overall favourable response; caspofungin (33.9 %) was as effective as liposomal amphotericin B (33.7 %) [% difference 0.2 (95.2 % CI –5.6, 6.0)]. An overall favourable response required meeting each of 5 criteria: (1) successful treatment of any baseline fungal infection (caspofungin 51.9 % [14/27], liposomal amphotericin B 25.9 % [7/27]), (2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment (caspofungin 94.8 % [527/556], liposomal amphotericin B 95.5 % [515/539]), (3) survival for 7 days after completion of study therapy (caspofungin 92.6 % [515/556], liposomal amphotericin B 89.2 % [481/539]), (4) no discontinuation from the study drug because of drug-related toxicity or lack of efficacy (caspofungin 89.7 % [499/556], liposomal amphotericin B 85.5 % [461/539]), and (5) resolution of fever during the period of neutropaenia (caspofungin 41.2 % [229/556], liposomal amphotericin B 41.4 % [223/539]). Response rates to caspofungin and liposomal amphotericin B for baseline infections caused by *Aspergillus* species were, respectively, 41.7 % (5/12) and 8.3 % (1/12), and by *Candida* species were 66.7 % (8/12) and 41.7 % (5/12). Patients in the caspofungin group experienced breakthrough infections due to the following uncommon yeasts and moulds: *Trichosporon* species (1), *Fusarium* species (1), *Mucor* species (1), and *Rhizopus* species (1).

5.2 Pharmacokinetic properties

Distribution

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

Metabolism

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

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

Elimination and excretion

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

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

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

Special populations

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Do not mix with diluents containing glucose, as CANCIDAS is not stable in diluents containing glucose. Do not mix or co-infuse CANCIDAS with other medicinal products, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products.

6.3 Shelf life

18 months

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

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

6.4 Special precautions for storage

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

For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

10 ml Type I glass vials with attached sterile transfer set closure for single use only.
Supplied in packs of 1 vial with 1 transfer set.

6.6 Special precautions for disposal

No special requirements.

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

Preparation of the daily 50-mg infusion (using vials with transfer set)
1. Bring the vial with transfer set to room temperature.
2. Remove the transfer set cap and link the vial to the port of a conventional 250 ml infusion bag of sterile sodium chloride for infusion, or lactated Ringer's solution. Reduced volume infusions in 100 ml may be used, when medically necessary for 50 mg daily doses. The transfer needle is enclosed in the

plastic needle guard. Simultaneously with insertion of the needle into the bag, back pressure causes the other end of the needle to pierce the vial stopper, allowing a free flow through the needle between the vial and the infusion bag.
3. The product is mixed by squeezing solvent in and out of the vial to effect dissolution, and the vial contents are allowed to drain back into the infusion bag. After full transfer, the vial and transfer set combination are removed from the infusion bag. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of last renewal

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 70 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 70 mg caspofungin (as acetate).

Each 70 mg vial contains 50.0 mg of sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white compact, lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive candidiasis in adult patients.
- 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.
- Empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus)* in febrile, neutropaenic adult patients.

4.2 Posology and method of administration

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

After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour. Do not mix or co-infuse CANCIDAS with other medicines, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products. DO NOT USE DILUENTS CONTAINING GLUCOSE, as CANCIDAS is not stable in diluents containing glucose. For reconstitution directions see section 6.6.

Both 70 mg and 50 mg vials are available.

A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, CANCIDAS 70 mg daily is recommended (see section 5.2). Doses higher than 70 mg daily have not been adequately studied.

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

Duration of treatment of invasive candidiasis should be based upon the patient's clinical and microbiological response. After signs and symptoms of invasive candidiasis have improved and

cultures have become negative, a switch to oral antifungal therapy may be considered. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

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

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

No dosage adjustment is necessary based on gender, race, or renal impairment (see section 5.2).

For mild hepatic insufficiency (Child-Pugh score 5 to 6), no dosage adjustment is needed. For patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), CANCIDAS 35 mg daily is recommended. An initial 70 mg loading dose should be administered on Day-1. There is no clinical experience with severe hepatic insufficiency (Child-Pugh score greater than 9) (see section 4.4).

The experience in children is limited.

Limited data suggest that an increase in the daily dose of CANCIDAS to 70 mg, following the 70 mg loading dose, should be considered when co-administering CANCIDAS with certain inducers of metabolic enzymes (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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

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

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

The safety information on treatment durations longer than 4 weeks is limited.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

4.6 Pregnancy and lactation

For CANCIDAS no clinical data on exposed pregnancies are available. Caspofungin should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of caspofungin in pregnant women. Developmental studies in animals have shown adverse effects (see section 5.3). Caspofungin has been shown to cross the placental barrier in animal studies. The potential risk to the human foetus is unknown.

Caspofungin is excreted in milk of lactating animals. It is not known whether it is excreted in human milk. Women receiving caspofungin should not breast-feed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In clinical studies, 1440 individuals received single or multiple doses of CANCIDAS: 564 febrile neutropaenic patients (empirical therapy study), 125 patients with invasive candidiasis, 72 patients with invasive aspergillosis, 285 patients with localised *Candida* infections, and 394 individuals enrolled in Phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation (including 39 allogeneic transplantations). In the studies involving patients with documented *Candida* infections, the majority of the patients with invasive *Candida* infections had serious underlying medical conditions (e.g., haematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the non-comparative *Aspergillus* study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications.

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

Reported clinical and laboratory abnormalities among all patients treated with CANCIDAS (total 989) were typically mild and rarely led to discontinuation.

The following adverse reactions were reported:

[Very common (≥1/10), Common (≥1/100, < 1/10)]

Blood and lymphatic system disorders:
Common: anaemia

Nervous system disorders:
Common: headache

Cardiac disorders:
Common: tachycardia

Vascular disorders:
Common: phlebitis/thrombophlebitis, flushing

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea

Gastrointestinal disorders:
Common: abdominal pain, nausea, diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Common: rash, pruritus, sweating

General disorders and administration site conditions:
Very common: fever
Common: pain, chills, infused-vein complications

Investigations:
Common: elevated liver values (AST, ALT, alkaline phosphatase, direct and total bilirubin), increased serum creatinine, decreased haemoglobin, decreased haematocrit, blood potassium decreased, hypomagnesaemia, low albumin, decreased white blood cells, increased eosinophils, platelet count decreased, decreased neutrophils, increased urinary red blood cells, increased partial thromboplastin time, decreased total serum protein, increased urinary protein, increased prothrombin time, blood

sodium decreased, increased urinary white blood cells and low calcium. High calcium has been reported as uncommon (≥1/1000, <1/100).

Possible histamine-mediated symptoms have been reported including reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Anaphylaxis has been reported during administration of caspofungin.

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

Post-Marketing experience:
The following post-marketing adverse events have been reported:

Hepatobiliary disorders:
Hepatic dysfunction

General disorders and administration site conditions:
Swelling and peripheral oedema

Investigations:
Hypercalcaemia

4.9 Overdose

Inadvertent administration of up to 140 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse experiences. Caspofungin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Caspofungin has *in vitro* activity against *Aspergillus* species (*Aspergillus fumigatus* [N = 75], *Aspergillus flavus* [N = 111], *Aspergillus niger* [N = 31], *Aspergillus nidulans* [N = 8], *Aspergillus terreus* [N = 52], and *Aspergillus candidus* [N = 3]). Caspofungin also has *in vitro* activity against *Candida* species (*Candida albicans* [N = 1032], *Candida dubliniensis* [N = 100], *Candida glabrata* [N = 151], *Candida guilliermondii* [N = 67], *Candida kefyr* [N = 62], *Candida krusei* [N = 147], *Candida lipolytica* [N = 20], *Candida lusitaniae* [N = 80], *Candida parapsilosis* [N = 215], *Candida rugosa* [N = 1], and *Candida tropicalis* [N = 258]), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-flucytosine. Susceptibility testing was performed according to a modification of both the National Committee for Clinical Laboratory Standards (NCCLS) method M38-A (for *Aspergillus* species) and method M27-A (for *Candida* species). Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment. However, standardised techniques for susceptibility testing for antifungal agents, including beta (1,3)-D-glucan synthesis inhibitors, have not been established. MIC values for caspofungin should not be used to predict clinical outcome, since a

correlation between MIC values and clinical outcome has not been established. Development of *in vitro* resistance to caspofungin by *Aspergillus* species has not been identified. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has not been observed. The incidence of resistance to caspofungin by various clinical isolates of *Candida* and *Aspergillus* is unknown.

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

Invasive Aspergillosis: Sixty-nine adult patients (age 18-80) with invasive aspergillosis were enrolled in an open-label, non-comparative study to evaluate the safety, tolerability, and efficacy of caspofungin. Patients had to be either refractory to (disease progression or failure to improve with other antifungal therapies given for at least 7 days) (84 % of the enrolled patients) or intolerant of (16 % of enrolled patients) other standard antifungal therapies. Most patients had underlying conditions (haematologic malignancy [N = 24], allogeneic bone marrow transplant or stem cell transplant [N = 18], organ transplant [N = 8], solid tumour [N = 3], or other conditions [N = 10]). Stringent definitions, modelled after the Mycoses Study Group Criteria, were used for diagnosis of invasive aspergillosis and for response to therapy (favourable response required clinically significant improvement in radiographs as well as in signs and symptoms). The mean duration of therapy was 33.7 days, with a range of 1 to 162 days. An independent expert panel determined that 41 % (26/63) of patients receiving at least one dose of caspofungin had a favourable response. For those patients who received more than 7 days of therapy with caspofungin, 50 % (26/52) had a favourable response. The favourable response rates for patients who were either refractory to or intolerant of previous therapies were 36 % (19/53) and 70 % (7/10), respectively. Although the doses of prior antifungal therapies in 5 patients enrolled as refractory were lower than those often administered for invasive aspergillosis, the favourable response rate during therapy with caspofungin was similar in these patients to that seen in the remaining refractory patients (2/5 versus 17/48, respectively). The response rates among patients with pulmonary disease and extrapulmonary disease were 47 % (21/45) and 28 % (5/18), respectively. Among patients with extrapulmonary disease, 2 of 8 patients who also had definite, probable, or possible CNS involvement had a favourable response.

Empirical Therapy in Febrile, Neutropaenic Adult Patients: A total of 1111 patients with persistent fever and neutropaenia were enrolled in a clinical study and treated with either caspofungin 50 mg once daily following a 70 mg loading dose or liposomal amphotericin B 3.0 mg/kg/day. Eligible patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation, and presented with neutropaenia (<500 cells/mm^3 for 96 hours) and fever (>38.0°C) not responding to ≥96 hours of parenteral antibacterial therapy. Patients were to be treated until up to 72 hours after resolution of neutropaenia, with a maximum duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated after 5 days of therapy, the dosage of study drug could be increased to 70 mg/day of caspofungin (13.3 % of patients treated) or to

5.0 mg/kg/day of liposomal amphotericin B (14.3 % of patients treated).There were 1095 patients included in the primary Modified Intention-To-Treat (MITT) efficacy analysis of overall favourable response; caspofungin (33.9 %) was as effective as liposomal amphotericin B (33.7 %) [% difference 0.2 (95.2 % CI –5.6, 6.0)]. An overall favourable response required meeting each of 5 criteria: (1) successful treatment of any baseline fungal infection (caspofungin 51.9 % [14/27], liposomal amphotericin B 25.9 % [7/27]), (2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment (caspofungin 94.8 % [527/556], liposomal amphotericin B 95.5 % [515/539]), (3) survival for 7 days after completion of study therapy (caspofungin 92.6 % [515/556], liposomal amphotericin B 89.2 % [481/539]), (4) no discontinuation from the study drug because of drug-related toxicity or lack of efficacy (caspofungin 89.7 % [499/556], liposomal amphotericin B 85.5 % [461/539]), and (5) resolution of fever during the period of neutropaenia (caspofungin 41.2 % [229/556], liposomal amphotericin B 41.4 % [223/539]). Response rates to caspofungin and liposomal amphotericin B for baseline infections caused by *Aspergillus* species were, respectively, 41.7 % (5/12) and 8.3 % (1/12), and by *Candida* species were 66.7 % (8/12) and 41.7 % (5/12). Patients in the caspofungin group experienced breakthrough infections due to the following uncommon yeasts and moulds: *Trichosporon* species (1), *Fusarium* species (1), *Mucor* species (1), and *Rhizopus* species (1).

5.2 Pharmacokinetic properties

Distribution

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

Metabolism

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

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

Elimination and excretion

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

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

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

Special populations

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Do not mix with diluents containing glucose, as CANCIDAS is not stable in diluents containing glucose. Do not mix or co-infuse CANCIDAS with other medicinal products, as there are no data available on the compatibility of CANCIDAS with other intravenous substances, additives, or medicinal products.

6.3 Shelf life

2 years

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

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

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

6.4 Special precautions for storage

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

For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

10 ml Type I glass vials with a grey butyl stopper and a plastic cap with a yellow/orange aluminium band, for single use only.
Supplied in packs of 1 vial.

6.6 Special precautions for disposal

No special requirements.

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

Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injections. The concentration of the reconstituted vial will be: 7 mg/ml.

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

Step 2 Addition of Reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, where medically necessary, for 35 mg daily doses. Do not use if the solution is cloudy or has precipitated. This infusion solution must be used within 24 hours if stored at or below 25°C, or within 48 hours if stored refrigerated at 2 to 8°C. Chemical and physical in-use stability of the diluted solution in sterile lactated Ringer's solution and sodium chloride solution 9 mg/ml (0.9 %), 4.5 mg/ml (0.45 %), and 2.25 mg/ml (0.225 %) for infusion has been demonstrated for 24 hours at 25°C and for 48 hours at 2 to 8°C. From a microbiological point of view, the solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

PREPARATION OF THE SOLUTION FOR INFUSION

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
70 mg	10 ml	0.27 mg/ml	Not recommended
70 mg (from two 50 mg vials)**	14 ml	0.27 mg/ml	Not recommended
35 mg for moderate hepatic insufficiency (from one 70 mg vial)	5 ml	0.14 mg/ml	0.33 mg/ml

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of last renewal

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

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

Merck Sharp & Dohme BV, Waarderweg 39, P.O. Box 581, 2003 PC Haarlem, The Netherlands

Manufacturing Authorisation issued on 21 March 2001 by the Ministry of Health, Welfare and Sport, the Public Health Supervisory Service, Inspectorate of Health Care, P.O. Box 16119, 2500 B.C. The Hague, The Netherlands.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

PSUR: The marketing Authorisation holder will continue to submit periodic safety update reports on a 2-year cycle.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 50 mg powder for concentrate for solution for infusion
Caspofungin (as acetate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 50 mg caspofungin (as acetate).

3. LIST OF EXCIPIENTS

Sucrose, mannitol, glacial acetic acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

CANCIDAS 50 mg powder for concentrate for solution for infusion
Caspofungin (as acetate)
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 50 mg powder for solution for infusion
Caspofungin (as acetate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 50 mg caspofungin (as acetate).

3. LIST OF EXCIPIENTS

Sucrose, mannitol, glacial acetic acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with transfer set

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/196/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

CANCIDAS 50 mg powder for solution for infusion
Caspofungin (as acetate)
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CANCIDAS 70 mg powder for concentrate for solution for infusion
Caspofungin (as acetate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 70 mg caspofungin (as acetate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

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6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

CANCIDAS 50 mg powder for concentrate for solution for infusion
Caspofungin (as acetate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CANCIDAS IS AND WHAT IT IS USED FOR

CANCIDAS is an antifungal medicine that interferes with the production of a component (glucan polysaccharide) of the fungal cell wall that is necessary if the fungus is to continue living and growing. Fungal cells exposed to CANCIDAS have incomplete or defective cell walls, making them fragile and unable to grow.

CANCIDAS may have been prescribed to treat a serious fungal infection called invasive candidiasis. The infection is caused by fungal (yeast) cells called *Candida*. These yeast cells are normally found in the digestive tract, and do not cause an infection unless they enter the bloodstream (in which case the infection is referred to as candidaemia) or other tissues or organs, such as the lining of the abdomen (peritonitis), the heart, the kidneys, the liver, bones, muscles, joints, spleen, or eyes. Persons at high risk for invasive candidiasis include surgical patients and those whose immune systems are deficient. Fever and chills that do not respond to antibacterial therapy are the most common symptoms of this type of infection.

Alternatively, your doctor may have prescribed CANCIDAS to treat a fungal infection in your nose, nasal sinuses, or lungs because other antifungal treatments have not been working as well as expected or because the other antifungal treatments are causing side effects. This infection is caused by organisms called *Aspergillus*. *Aspergillus* fungal infections begin in the respiratory system (in the nose, sinuses, or lungs) because the spores of the fungus are found in the air we breathe every day. This infection is named invasive aspergillosis. It is possible for the fungus to spread to other tissues and organs. In most healthy individuals, the natural ability to fight disease destroys the spores and removes them from the body. Some medical conditions lower the body's resistance to diseases. Also, certain medicines prescribed for patients who are organ or bone marrow recipients lower the body's resistance to diseases. These are the patients who are most likely to develop an *Aspergillus* infection.

Persistent fever due to infection may occur following chemotherapy or medical conditions that lower the body's resistance to disease by lowering counts of certain white blood cells. If the fever is not reduced by treatment with an antibiotic, your doctor may suspect that you have a fungal infection and prescribe CANCIDAS to treat it.

2. BEFORE YOU TAKE CANCIDAS

Do not take CANCIDAS

- if you are hypersensitive (allergic) to caspofungin or any of the other ingredients of CANCIDAS.

Take special care with CANCIDAS

- if you have had or now have liver problems. Some patients with liver problems may require a dosage adjustment.
- if you are taking cyclosporin, a medicine to help prevent organ transplant rejection or to treat certain problems with your immune system. Your physician may order additional blood tests during your treatment.
- if you have any allergies.

Tell your doctor about any medical conditions you have or have had.

Children

CANCIDAS should not be used in patients under 18 years of age.

Taking other medicines

Your physician will determine if any adjustments should be made to other medicines you may be taking. If you are receiving cyclosporine, your physician may order additional blood tests during your treatment.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important for your doctor to know if you are taking certain anti-HIV medicines (including efavirenz or nevirapine), the antiseizure (epilepsy) medicines phenytoin and carbamazepine, the steroid dexamethasone, the antibiotic rifampicin, and the immunosuppressant tacrolimus.

Pregnancy and breastfeeding

CANCIDAS has not been studied in pregnant women, and should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.
Women receiving CANCIDAS should not breast-feed.
Ask you doctor for advice before taking any medicine.

Driving and using machines

There is no information to suggest that CANCIDAS affects your ability to drive or operate machinery.

Important information about some of the ingredients of CANCIDAS

CANCIDAS contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE CANCIDAS

CANCIDAS will always be prepared and given to you by a doctor or another healthcare professional.

CANCIDAS should be administered once daily by slow intravenous infusion over approximately 1 hour.

Your physician will determine the duration of your treatment and how much CANCIDAS you will receive each day. He will monitor your response and condition. The dose will not need to be adjusted according to your age or if you are suffering from renal impairment. If you weigh more than 80 kg, a dose adjustment may be required.

If you take more CANCIDAS than you should

Your doctor will monitor your response and condition to determine what CANCIDAS treatment is needed. However, if you are concerned that you may have been given too much CANCIDAS, contact your doctor or another healthcare professional immediately.

If you miss/forget to take a dose of CANCIDAS

Your doctor will monitor your response and condition to determine what CANCIDAS treatment is needed. However, if you are concerned that you may have missed a dose, contact your doctor or another healthcare professional immediately.

If you stop taking CANCIDAS

There are no known withdrawal symptoms.

4. POSSIBLE SIDE EFFECTS

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

The following terms are used to describe how often side effects have been reported.

Very Common (occurring in at least 1 in 10 patients treated)
Common (occurring in at least 1 of 100 and less than 1 of 10 patients treated)
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Not known (cannot be estimated from the available data)

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Common: headache

Cardiac disorders:
Common: rapid heart beat
Not known: swelling of the hands, ankles or feet,

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Respiratory, thoracic and mediastinal disorders:
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Gastrointestinal disorders:
Common: stomach pain, nausea, vomiting, diarrhoea.

Skin and subcutaneous tissue disorders:
Common: rash, itching, sweating,

General disorders and administration site conditions:

Very common: fever
Common: pain, chills, vein irritations at the infusion site (including itching, redness, discharge, swelling, burning sensation, or clotting),

Hepato biliary disorders
Rare**:** impaired liver function

Investigations:
Common: alterations in some laboratory blood tests (including decreased red blood cell count and increased values of some liver and kidney tests,
Uncommon: high calcium

Possible histamine-mediated symptoms have been reported including reports of rash, swelling of the face and/or lips, itching, sensation of warmth, or trouble breathing.

Life-threatening allergic reactions that might include difficulty breathing with wheezing or worsening of an existing rash have been reported rarely during administration of CANCIDAS. Other side effects may also occur rarely, and as with any prescription medicine, some side effects may be serious. Ask your doctor for more information.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CANCIDAS

Keep out of the reach and sight of children.

Do not use CANCIDAS after the expiry date which is stated on the carton and the vial. The first 2 numbers indicate the month; the next 4 numbers indicate the year. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Reconstituted CANCIDAS should be used immediately because it does not contain any preservatives to prevent bacterial contamination. Only a trained health care professional who has read the complete directions (please see below “Instructions of how to reconstitute and dilute CANCIDAS”) can properly prepare this medicine for use.

6. FURTHER INFORMATION

What CANCIDAS contains
The active substance of CANCIDAS is caspofungin (as acetate).
The other ingredients are: sucrose, mannitol, glacial acetic acid, and sodium hydroxide.

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

Each pack contains one vial containing 50 mg Caspofungin (as acetate).

Marketing Authorisation Holder and Manufacturer

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Product Manufacturer
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This leaflet was last approved in

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

Instructions of how to reconstitute and dilute CANCIDAS:

Reconstitution of CANCIDAS

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

Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injections. The concentrations of the reconstituted vials will be: 5 mg/ml.

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

Step 2 Addition of Reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or has precipitated. This infusion solution must be used within 24 hours if stored at or below 25°C, or within 48 hours if stored refrigerated at 2 to 8°C. Chemical and physical in-use stability of the diluted solution in sterile lactated Ringer's solution and sodium chloride solution 9 mg/ml (0.9 %), 4.5 mg/ml (0.45 %), and 2.25 mg/ml (0.225 %) for infusion has been demonstrated for 24 hours at 25°C and for 48 hours at 2 to 8°C. From a microbiological point of view, the solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

PREPARATION OF THE SOLUTION FOR INFUSION

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
50 mg	10 ml	0.19 mg/ml	-
50 mg at reduced volume	10 ml	-	0.45 mg/ml
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 ml	0.14 mg/ml	-
35 mg for moderate hepatic insufficiency (from one 50 mg vial) at reduced volume	7 ml	-	0.33 mg/ml

* 10.5 ml should be used for reconstitution of all vials

PACKAGE LEAFLET: INFORMATION FOR THE USER

CANCIDAS 50 mg powder for solution for infusion
Caspofungin (as acetate)

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CANCIDAS may have been prescribed to treat a serious fungal infection called invasive candidiasis. The infection is caused by fungal (yeast) cells called *Candida*. These yeast cells are normally found in the digestive tract, and do not cause an infection unless they enter the bloodstream (in which case the infection is referred to as candidaemia) or other tissues or organs, such as the lining of the abdomen (peritonitis), the heart, the kidneys, the liver, bones, muscles, joints, spleen, or eyes. Persons at high risk for invasive candidiasis include surgical patients and those whose immune systems are deficient. Fever and chills that do not respond to antibacterial therapy are the most common symptoms of this type of infection.

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Take special care with CANCIDAS

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- if you are taking cyclosporine, a medicine to help prevent organ transplant rejection or to treat certain problems with your immune system. Your physician may order additional blood tests during your treatment.
- if you have any allergies.

Tell your doctor about any medical conditions you have or have had.

Children

CANCIDAS should not be used in patients under 18 years of age.

Taking other medicines

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Ask you doctor for advice before taking any medicine.

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There is no information to suggest that CANCIDAS affects your ability to drive or operate machinery.

Important information about some of the ingredients of CANCIDAS

CANCIDAS contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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If you take more CANCIDAS than you should

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If you miss/forget to take a dose of CANCIDAS

Your doctor will monitor your response and condition to determine what CANCIDAS treatment is needed. However, if you are concerned that you may have missed a dose, contact your doctor or another healthcare professional immediately.

If you stop taking CANCIDAS

There are no known withdrawal symptoms.

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

The following terms are used to describe how often side effects have been reported.

Very Common (occurring in at least 1 in 10 patients treated)
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Common: headache

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Common: pain, chills, vein irritations at the infusion site (including itching, redness, discharge, swelling, burning sensation, or clotting),

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Investigations:
Common: alterations in some laboratory blood tests (including decreased red blood cell count and increased values of some liver and kidney tests,
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Possible histamine-mediated symptoms have been reported including reports of rash, swelling of the face and/or lips, itching, sensation of warmth, or trouble breathing.

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The other ingredients are: sucrose, mannitol, glacial acetic acid, and sodium hydroxide.

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Instructions of how to reconstitute CANCIDAS:

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

Preparation of the daily 50-mg infusion (using vials with transfer set)
1. Bring the vial with transfer set to room temperature.
2. Remove the transfer set cap and link the vial to the port of a conventional 250 ml infusion bag of sterile sodium chloride for infusion, or lactated Ringer's solution. Reduced volume infusions in 100 ml may be used, when medically necessary for 50 mg daily doses. The transfer needle is enclosed in the plastic needle guard. Simultaneously with insertion of the needle into the bag, back pressure causes the other end of the needle to pierce the vial stopper, allowing a free flow through the needle between the vial and the infusion bag.
3. The product is mixed by squeezing solvent in and out of the vial to effect dissolution, and the vial contents are allowed to drain back into the infusion bag. After full transfer, the vial and transfer set combination are removed from the infusion bag. This infusion solution must be used within 24 hours if stored at or below 25°C or within 48 hours if stored refrigerated at 2 to 8°C.

PACKAGE LEAFLET: INFORMATION FOR THE USER

CANCIDAS 70 mg powder for concentrate for solution for infusion
Caspofungin (as acetate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CANCIDAS IS AND WHAT IT IS USED FOR

CANCIDAS is an antifungal medicine that interferes with the production of a component (glucan polysaccharide) of the fungal cell wall that is necessary if the fungus is to continue living and growing. Fungal cells exposed to CANCIDAS have incomplete or defective cell walls, making them fragile and unable to grow.

CANCIDAS may have been prescribed to treat a serious fungal infection called invasive candidiasis. The infection is caused by fungal (yeast) cells called *Candida*. These yeast cells are normally found in the digestive tract, and do not cause an infection unless they enter the bloodstream (in which case the infection is referred to as candidaemia) or other tissues or organs, such as the lining of the abdomen (peritonitis), the heart, the kidneys, the liver, bones, muscles, joints, spleen, or eyes. Persons at high risk for invasive candidiasis include surgical patients and those whose immune systems are deficient. Fever and chills that do not respond to antibacterial therapy are the most common symptoms of this type of infection.

Alternatively, your doctor may have prescribed CANCIDAS to treat a fungal infection in your nose, nasal sinuses, or lungs because other antifungal treatments have not been working as well as expected or because the other antifungal treatments are causing side effects. This infection is caused by organisms called *Aspergillus*. *Aspergillus* fungal infections begin in the respiratory system (in the nose, sinuses, or lungs) because the spores of the fungus are found in the air we breathe every day. This infection is named invasive aspergillosis. It is possible for the fungus to spread to other tissues and organs. In most healthy individuals, the natural ability to fight disease destroys the spores and removes them from the body. Some medical conditions lower the body's resistance to diseases. Also, certain medicines prescribed for patients who are organ or bone marrow recipients lower the body's resistance to diseases. These are the patients who are most likely to develop an *Aspergillus* infection.

Persistent fever due to infection may occur following chemotherapy or medical conditions that lower the body's resistance to disease by lowering counts of certain white blood cells. If the fever is not reduced by treatment with an antibiotic, your doctor may suspect that you have a fungal infection and prescribe CANCIDAS to treat it.

2. BEFORE YOU TAKE CANCIDAS

Do not take CANCIDAS

- if you are hypersensitive (allergic) to caspofungin or any of the other ingredients of CANCIDAS.

Take special care with CANCIDAS

- if you have had or now have liver problems. Some patients with liver problems may require a dosage adjustment.
- if you are taking cyclosporin, a medicine to help prevent organ transplant rejection or to treat certain problems with your immune system. Your physician may order additional blood tests during your treatment.
- if you have any allergies.

Tell your doctor about any medical conditions you have or have had.

Children

CANCIDAS should not be used in patients under 18 years of age.

Taking other medicines

Your physician will determine if any adjustments should be made to other medicines you may be taking. If you are receiving cyclosporine, your physician may order additional blood tests during your treatment.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important for your doctor to know if you are taking certain anti-HIV medicines (including efavirenz or nevirapine), the antiseizure (epilepsy) medicines phenytoin and carbamazepine, the steroid dexamethasone, the antibiotic rifampicin, and the immunosuppressant tacrolimus.

Pregnancy and breastfeeding

CANCIDAS has not been studied in pregnant women, and should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus

Women receiving CANCIDAS should not breast-feed.
Ask you doctor for advice before taking any medicine.

Driving and using machines

There is no information to suggest that CANCIDAS affects your ability to drive or operate machinery.

Important information about some of the ingredients of CANCIDAS

CANCIDAS contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE CANCIDAS

CANCIDAS will always be prepared and given to you by a doctor or another healthcare professional.

CANCIDAS should be administered once daily by slow intravenous infusion over approximately 1 hour.

Your physician will determine the duration of your treatment and how much CANCIDAS you will receive each day. He will monitor your response and condition. The dose will not need to be adjusted according to your age or if you are suffering from renal impairment. If you weigh more than 80 kg, a dose adjustment may be required.

If you take more CANCIDAS than you should

Your doctor will monitor your response and condition to determine what CANCIDAS treatment is needed. However, if you are concerned that you may have been given too much CANCIDAS, contact your doctor or another healthcare professional immediately.

If you miss/forget to take a dose of CANCIDAS

Your doctor will monitor your response and condition to determine what CANCIDAS treatment is needed. However, if you are concerned that you may have missed a dose, contact your doctor or another healthcare professional immediately.

If you stop taking CANCIDAS
There are no known withdrawal symptoms.

4. POSSIBLE SIDE EFFECTS

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

The following terms are used to describe how often side effects have been reported.

Very Common (occurring in at least 1 in 10 patients treated)
Common (occurring in at least 1 of 100 and less than 1 of 10 patients treated)
Uncommon (occurring in at least 1of 1000 and less than 1 of 100 patients treated)
Rare (occurring in at least 1 of 10,000 and less than 1 of 1000 patients treated)
Not known (cannot be estimated from the available data)

Nervous system disorders:
Common: headache

Cardiac disorders:
Common: rapid heart beat
Not known: swelling of the hands, ankles or feet,

Vascular disorders:
Common: flushing

Respiratory, thoracic and mediastinal disorders:
Common: shortness of breath

Gastrointestinal disorders:
Common: stomach pain, nausea, vomiting, diarrhoea.

Skin and subcutaneous tissue disorders:
Common: rash, itching, sweating,

General disorders and administration site conditions:
Very common: fever

Common: pain, chills, vein irritations at the infusion site (including itching, redness, discharge, swelling, burning sensation, or clotting),

Hepato biliary disorders
Rare**:** impaired liver function

Investigations:
Common: alterations in some laboratory blood tests (including decreased red blood cell count and increased values of some liver and kidney tests,
Uncommon: high calcium

Possible histamine-mediated symptoms have been reported including reports of rash, swelling of the face and/or lips, itching, sensation of warmth, or trouble breathing.

Life-threatening allergic reactions that might include difficulty breathing with wheezing or worsening of an existing rash have been reported rarely during administration of CANCIDAS. Other side effects may also occur rarely, and as with any prescription medicine, some side effects may be serious. Ask your doctor for more information.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CANCIDAS

Keep out of the reach and sight of children.

Do not use CANCIDAS after the expiry date which is stated on the carton and the vial. The first 2 numbers indicate the month; the next 4 numbers indicate the year. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Reconstituted CANCIDAS should be used immediately because it does not contain any preservatives to prevent bacterial contamination. Only a trained health-care professional who has read the complete directions (please see below “Instructions of how to reconstitute and dilute CANCIDAS”) can properly prepare this medicine for use.

6. FURTHER INFORMATION

What CANCIDAS contains
The active substance of CANCIDAS is caspofungin (as acetate).
The other ingredients are: sucrose, mannitol, glacial acetic acid, and sodium hydroxide.

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

Each pack contains one vial containing 70 mg Caspofungin (as acetate).

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder	**Product Manufacturer**
Merck Sharp & Dohme Limited	Merck Sharp & Dohme B. V.
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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Step 1 Reconstitution of conventional vials
To reconstitute the powder bring the vial to room temperature and aseptically add 10.5 ml of water for injections. The concentration of the reconstituted vial will be: 7 mg/ml.

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

Step 2 Addition of reconstituted CANCIDAS to patient infusion solution
Diluents for the final solution for infusion are: sodium chloride solution for injection, or lactated Ringer's solution. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion bag or bottle. Reduced volume infusions in 100 ml may be used, where medically necessary, for 35 mg daily doses. Do not use if the solution is cloudy or has precipitated. This infusion solution must be used within 24 hours if stored at or below 25°C, or within 48 hours if stored refrigerated at 2 to 8°C. Chemical and physical

in-use stability of the diluted solution in sterile lactated Ringer's solution and sodium chloride solution 9 mg/ml (0.9 %), 4.5 mg/ml (0.45 %), and 2.25 mg/ml (0.225 %) for infusion has been demonstrated for 24 hours at 25°C and for 48 hours at 2 to 8°C. From a microbiological point of view, the solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

PREPARATION OF THE SOLUTION FOR INFUSION

DOSE*	**Volume of reconstituted CANCIDAS for transfer to intravenous bag or bottle**	**Standard preparation** (reconstituted CANCIDAS added to 250 ml) final concentration	**Reduced volume infusion** (reconstituted CANCIDAS added to 100 ml) final concentration
70 mg	10 ml	0.27 mg/ml	not recommended
70 mg (from two 50-mg vials)**	14 ml	0.27 mg/ml	not recommended
35 mg for moderate hepatic insufficiency (from one 70 mg vial)	5 ml	0.14 mg/ml	0.33 mg/ml

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