CANCIDAS® 50 mg powder for concentrate for solution for infusion (caspofungin acetate)
CANCIDAS® 70 mg powder for concentrate for solution for infusion (caspofungin acetate)

PRESCRIBING INFORMATION
Refer to Summary of Product Characteristics before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD (tel: 01992-467272), UK.

PRESENTATION
50 mg vial: Before reconstitution, each vial contains a white to off-white compact powder containing 50 mg caspofungin.
70 mg vial: Before reconstitution, each vial contains a white to off-white compact powder containing 70 mg caspofungin.

USES
Treatment of invasive candidiasis in adult or paediatric patients. Treatment of invasive aspergillosis in adult or paediatric 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, neutropenic adult or paediatric patients.

DOSAGE AND ADMINISTRATION
Caspofungin should be initiated by a physician experienced in the management of invasive fungal infections.

Posology
Adult patients
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, caspofungin 70 mg daily is recommended. No dosage adjustment is necessary based on gender or race.
Paediatric patients (12 months to 17 years)
In paediatric patients (12 months to 17 years of age), dosing should be based on the patient's body surface area. For all indications, a single 70 mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). The daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) in those patients whom the 50 mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response.

Caution is advised when treating neonates and infants below 12 months of age as the efficacy and safety of caspofungin have not been sufficiently studied in this age group. Consider caspofungin at 25 mg/m^2 daily in neonates and infants (less than 3 months of age) and 50 mg/m^2 daily in young children (3 to 11 months of age).

Duration of treatment
Duration of empirical therapy should be based on the patient's clinical response. Continue therapy until up to 72 hours after resolution of neutropenia (ANC≥ 500). Treat patients found to have a fungal infection for at least 14 days and continue treatment for at least 7 days after both neutropenia 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, consider a switch to oral antifungal therapy. In general, continue antifungal therapy 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 based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. In general, continue treatment for at least 7 days after resolution of symptoms.

Safety information on treatment durations longer than 4 weeks is limited. However, available data suggest that caspofungin continues to be well tolerated with longer courses of therapy (up to 162 days in adult patients and up to 87 days in paediatric patients).

Special populations
Elderly patients (65 years of age or more): No dosage adjustment required. There is limited treatment experience in patients 65 years of age and older. *Renal impairment*: No dosage adjustment necessary. *Hepatic impairment:* For adult patients with mild hepatic impairment, no dosage adjustment is needed. For adult patients with moderate hepatic impairment, caspofungin 35 mg daily is recommended. Administer an initial 70 mg loading dose on day 1. There is no clinical experience in adult patients with severe hepatic impairment and in paediatric patients with any degree of hepatic impairment. A higher exposure than in moderate hepatic impairment is expected and caspofungin should be used with caution in these patients.
'Cancidas' contains sucrose. Patients with rare hereditary problems of fructose intolerance or sucrase-isomaltase insufficiency should not take this medicinal product.

When co-administering caspofungin in adult patients with certain inducers of metabolic enzymes, consider an increase in the daily dose to 70 mg, following the 70 mg loading dose.
When caspofungin is co-administered to paediatric patients (12 months to 17 years of age) with these same inducers of metabolic enzymes, a dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

Method of administration
After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour.
Do not mix caspofungin with other medicines. DO NOT USE DILUENTS CONTAINING GLUCOSE. For reconstitution directions, see SPC.

Caspofungin should be given as a single daily infusion.

CONTRA-INDICATIONS
Hypersensitivity to caspofungin acetate or to any of the excipients.

PRECAUTIONS
Anaphylaxis and possible histamine-mediated adverse reactions (which may include; rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm) have been reported with the use of caspofungin. If this occurs, discontinue use and administer appropriate supportive treatment as necessary.

Concomitant use with ciclosporin has been evaluated in healthy adult volunteers and in adult patients and the data suggest that caspofungin can be used in patients receiving ciclosporin when the potential benefit outweighs the potential risk. Consider close monitoring of liver enzymes with concomitant use.

Cases of Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported. Exercise caution in patients with history of allergic skin reaction.

Safety information on treatment of longer than 4 weeks is limited.

Drug interactions
Ciclosporin: In healthy adult subjects, ciclosporin A increased the AUC of caspofungin by 35% and transiently increased liver ALT and AST levels (see 'Precautions'). Caspofungin did not increase plasma levels of ciclosporin. *Tacrolimus:* Caspofungin reduced the trough concentration of tacrolimus in healthy adult volunteers. For patients receiving both therapies, monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are mandatory. In healthy adult volunteers the pharmacokinetics of caspofungin was not altered to a clinically relevant extent by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus. 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. *Rifampicin:* Rifampicin caused a 60% increase in AUC and 170% increase in trough concentration of caspofungin on the first day of co-administration when both drugs were initiated together in healthy adult volunteers. After two weeks repeated co-administration rifampicin had little effect on AUC, but caspofungin trough levels were 30% lower than in adult subjects who received caspofungin alone. Similar effects might be expected for other metabolic enzyme inducers. When co-administering with inducers of metabolic enzymes, consider for adult patients an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose.
The interaction of caspofungin doses higher than 50 or 70 mg daily with other medications has not been formally studied. Data may indicate that paediatric patients will have similar reductions with inducers as adults. When co-administering to paediatric patients (12 months to 17 years of age) with inducers of drug clearance, consider a dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg).

Fertility, pregnancy & lactation: There are no or limited data from the use of caspofungin in pregnant women. Caspofungin should not be used during pregnancy unless clearly necessary. Caspofungin has been shown to cross the placental barrier in animal studies. It is unknown whether caspofungin is excreted in human milk. Available pharmacodynamic/ toxicological data in animals have shown excretion of caspofungin in milk. Women receiving caspofungin should not breast-feed. There are no clinical data for caspofungin to assess its impact on fertility.

SIDE EFFECTS

Refer to SPC for complete information on side effects.

Hypersensitivity reactions (anaphylaxis and possibly histamine-mediated adverse reactions) have been reported.

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

<u>*Adult patients*</u>

Phlebitis was a commonly reported local injection-site adverse reaction in all patients. Other local reactions included erythema, pain/tenderness, itching, discharge, and a burning sensation. Reported clinical and laboratory abnormalities among all adult patients treated with caspofungin (total 1,780) were typically mild and rarely led to discontinuation.

The following adverse reactions were reported:

Very common (*[≥1/10]*):
General disorders and administration site conditions: fever.

Common (*[≥1/100 to <1/10]*):
Blood and lymphatic disorders: haemoglobin decreased, haematocrit decreased, white blood cell count decreased; *Metabolism and nutrition disorders:* hypokalaemia; *Nervous system disorders:* headache; *Vascular disorders:* phlebitis; *Respiratory, thoracic and mediastinal disorders:* dyspnoea; *Gastro-intestinal disorders:* nausea, diarrhoea, vomiting; *Hepatobiliary disorders:* elevated liver values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, bilirubin conjugated, blood bilirubin); *Skin and subcutaneous tissue disorders:* rash, pruritus, erythema, hyperhidrosis; *Musculoskeletal and connective tissue disorders:* arthralgia; *General disorders and administration site conditions*: pyrexia, chills, infusion-site pruritus.

Uncommon and serious (≥1/1,000 to <1/100)
Blood and lymphatic disorders: anaemia, thrombocytopaenia, coagulopathy, leukopaenia, eosinophil count increased, platelet count decreased, platelet count increased, lymphocyte count decreased, white blood cell count increased, neutrophil count decreased; *Metabolism and nutrition disorders:* fluid overload, hypomagnesaemia, electrolyte imbalance, hyperglycaemia, hypocalcaemia, metabolic acidosis; *Cardiac disorders:* palpitations, tachycardia, arrhythmia, atrial fibrillation, cardiac failure congestive; *Vascular disorders:* hypertension, hypotension; *Respiratory, thoracic and mediastinal disorders:*, tachypnoea, bronchospasm, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing; *Hepatobiliary disorders:* cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, hepatic function abnormal, hepatotoxicity, liver disorder, gamma-glutamyltransferase increased; *Renal and urinary disorders:* renal failure, renal failure acute; *General disorders and administration site conditions:* oedema peripheral, chest discomfort, chest pain, oedema.

Frequency unknown and serious
Skin and subcutaneous tissue disorders: toxic epidermal necrosis and Steven-Johnson Syndrome.

Investigations:
Common: blood potassium decreased, blood albumin decreased. *Uncommon:* blood creatinine increased, red blood cells urine positive, protein total decreased, protein urine present, prothrombin time prolonged, prothrombin time shortened, blood sodium decreased, blood sodium increased, blood calcium decreased, blood calcium increased, blood chloride decreased, blood glucose increased, blood magnesium decreased, blood phosphorus decreased, blood phosphorus increased, blood urea increased, activated partial thromboplastin time prolonged, blood bicarbonate decreased, blood chloride increased, blood potassium increased, blood pressure increased, blood uric acid decreased, blood urine present, breath sounds abnormal, carbon dioxide decreased, immunosuppressant drug level increased, international normalised ratio increased, urinary casts, white blood cells urine positive, and pH urine increased.

<u>*Paediatric patients*</u>

Data from 5 clinical studies completed in 171 paediatric patients suggest that the overall

incidence of clinical adverse experiences is not worse than reported for adults treated with caspofungin. However, paediatric patients probably have a different adverse event profile compared to adult patients. The most common drug-related clinical adverse experiences reported in paediatric patients treated with caspofungin were pyrexia (11.7%), rash (4.7%) and headache (2.9%).

The following adverse reactions were reported:
Very common (*[≥1/10]*):
General disorders and administration site conditions: fever.
Common (*[≥1/100 to <1/10]*):
Blood and lymphatic system disorders: eosinophil count increased; *Nervous system disorders:* headache; *Cardiac disorders:* tachycardia; *Vascular disorders:* flushing, hypotension; *Hepatobiliary disorders:* elevated liver enzyme levels (AST, ALT); *Skin and subcutaneous tissue disorders:* rash, pruritus; *General disorders and administration site conditions:* chills, catheter site pain.

Investigations:
Common: decreased potassium, hypomagnesaemia, increased glucose, decreased phosphorus, and increased phosphorus

The following post-marketing adverse reactions have been reported: hepatic dysfunction, swelling and peripheral oedema, hypercalcaemia.

PACKAGE QUANTITIES AND BASIC NHS COST
50 mg vial £327.67
70 mg vial £416.78

Marketing Authorisation numbers:
50 mg vial EU/1/01/196/001
70 mg vial EU/1/01/196/003

Marketing Authorisation holder:
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

Legal Category: POM

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