



Caspofungin

ASCANEX

50mg Lyophilized Powder
for Solution for Infusion
Antifungal



Caspofungin Acetate
1313001346-00

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FORMULATION:

Each vial contains:
Caspofungin Acetate is equivalent to Caspofungin 50mg
Excipients q.s.

INDICATIONS:

- 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, neutropaenic adult or paediatric patients.

DOSAGE AND ADMINISTRATION:

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

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 and 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 (see Instructions for Use in Paediatric Patients, Mosteller Formula). For all indications, a single 70-mg/m² loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50mg/m² daily thereafter (not to exceed an actual dose of 70 mg daily). If the 50-mg/m² daily dose is well tolerated but does not provide and adequate clinical response, the daily dose can be increased to 70 mg/m² daily (not to exceed an actual daily dose of 70 mg).

The safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age. Caution is advised when treating this age group. Limited data suggest that caspofungin at 25 mg/m² daily in neonates and infants (less than 3 months of age) and 50 mg/m² daily in young children (3 to 11 months of age) can be considered.

Duration of Treatment

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 neutropenia (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 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, a switch to oral antifungal therapy may be considered. In general, antifungal therapy should continue for at least 14days 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.

DIRECTIONS FOR RECONSTITUTION:

To reconstitute the powder, bring the vial to room temperature and aseptically add 10.5 ml of water for injection.

Special populations

Elderly patients

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.

Renal impairment

No dosage adjustment is necessary based on renal impairment.

Hepatic impairment

For adult patients with mild hepatic impairment (Child-Pugh score 5-6), no dosage adjustment is needed. For adult patients with moderate hepatic impairment (Child-Pugh score 7-9), caspofungin 35 mg daily is recommended based upon pharmacokinetic data. An initial 70 mg loading dose should be administered on Day-1. There is no clinical experience in adult patients with severe hepatic impairment (Child-Pugh score greater than 9) and in paediatric patients with any degree of hepatic impairment.

Co-administration with inducers of metabolic enzymes

Limited data suggest that an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered when co-administering caspofungin in adult patients with certain inducers of metabolic enzymes. When caspofungin is co-administered to paediatric patients (12 months to 17 years of age) with these same inducers of metabolic enzymes, a caspofungin dose of 70-mg/m² 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.

Caspofungin should be given as a single daily infusion.

CONTRAINDICATIONS:

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Anaphylaxis has been reported during administration of caspofungin. If this occurs, caspofungin should be discontinued and appropriate treatment administered. Possibly histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasms have been reported and may require discontinuation and/or administration of appropriate treatment.

Limited data suggest that less common non-Candida yeasts and non-aspergillus moulds are not covered by caspofungin against these fungal pathogens has not been established

Concomitant use of caspofungin with ciclosporin has been evaluated in healthy adult volunteers and in adult patients. Some healthy adult volunteers who received two 3 mg/kg doses of ciclosporin 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 caspofungin and ciclosporin for 1 to 290 days (median 17.5 days), no serious hepatic adverse events were noted. These data suggest that caspofungin can be used in patients receiving ciclosporin when the potential benefit outweighs the potential risk. Close monitoring of liver enzymes should be considered if caspofungin and ciclosporin are used concomitantly.

In adult 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 for adults with moderate hepatic impairment. There is no clinical experience in adults with severe hepatic impairment or 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.

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and paediatric patients treated with caspofungin. In some adult and paediatric patients with serious underlying conditions who were receiving multiple concomitant medications with caspofungin, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported; a causal relationship to caspofungin has not been established. Patients who develop abnormal liver function tests during caspofungin therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing caspofungin therapy should be re-evaluated.

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

Drug Interactions:

Studies in vitro show that caspofungin 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.

In two clinical studies performed in healthy adult subjects, ciclosporin 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. Caspofungin did not increase the plasma levels of ciclosporin. There were transient increases in liver ALT and AST of less than or equal to 3-fold the upper limit of normal (ULN) when caspofungin and ciclosporin were co-administered, that resolved with discontinuation of the medicinal products. In a retrospective study of 40 patients treated during marketed use with caspofungin and ciclosporin for 1 to 290 days (median 17.5 days), no serious hepatic adverse reactions were noted. Close monitoring of liver enzymes should be considered if the two medicinal products are used concomitantly.

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

Clinical studies in healthy adult volunteers show that the pharmacokinetics of caspofungin are not altered to a clinically relevant extent by itraconazole, amphotericin B, mycophenolate, neftinavir, 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, neftinavir or mycophenolate mofetil are co-administered with caspofungin.

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 in healthy adult volunteers. 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 adult 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 caspofungin 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 caspofungin to 70 mg, following the 70 mg loading dose should be considered in adult patients.

All adult drug-drug interaction studies described above were conducted at a 50 or 70 mg daily caspofungin dose. The interaction of higher doses of caspofungin with other medicinal products has not been formally studied.

In paediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with caspofungin may result in clinically meaningful reductions in caspofungin trough concentrations. This finding may indicate that paediatric patients will have similar reductions with inducers as seen in adults. When caspofungin is co-administered to paediatric patients (12 months to 17 years of age) with inducers of drug clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a caspofungin dose of 70-mg/m² daily (not to exceed an actual daily dose of 70 mg) should be considered.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no or limited data from the use of caspofungin in pregnant women. Caspofungin should not be used during pregnancy unless clearly necessary. Animal studies have shown developmental toxicity. Caspofungin has been shown to cross the placental barrier in animal studies.

Breast-feeding

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.

Fertility

For caspofungin, there were no effects on fertility in studies conducted in male and female rats. There are no clinical data for caspofungin to assess its impact on fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDERSIRABLE EFFECTS

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

OVERDOSE

Inadvertent administration of up to 400 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse reactions. Caspofungin is not dialysable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: antimycotics for systematic use. ATC Code: J02AX04

Mechanism of action

Caspofungin acetate is a semi-synthetic lipopeptide (echinocandin) compound synthesized 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 hyphalalical tips and branch points where cell growth and division occur.

Pharmacodynamic effects

Caspofungin has in vitro activity against Aspergillus species (Aspergillus fumigatus (N=75), Aspergillus nigar (N=311, Aspergillus nidulans (N = 8), Aspergillus terreus (N=52), and Aspergillus candidus IN-3]. Caspofungin also has in vitro activity against Candida species (Candida albicans (N = 1,0321, Candida dubliniensis [N-1001, Candida glabrata (N-1511, Candida guilliermondi IN=67], Candida kefyr (N=62), Candida krusei (N=147), Candida lipolytica (N = 20), Candida lusitanae (N=80), Candida parapsilesis [N=215], Candida rugosa (N = 1), and Candida tropicalis IN-258]), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-fluocytosine. Susceptibility testing was performed according to a modification of both the Clinical and Laboratory Standards Institute (CLSI, formerly known as the National Committee for Clinical Laboratory Standards [NCCLS]) method M38-A2 (for Aspergillus species) and method M27-A3 (for Candida species). Standardised techniques for susceptibility testing have been established for yeasts by EUCAST. However, interpretive breakpoints for caspofungin have not been approved by EUCAST. Isolates of Candida with reduced susceptibility to caspofungin have been identified in a small number of patients during treatment (MICs for caspofungin >2 mg/l (4- to 30-fold MIC increases) have been reported using standardized MIC testing techniques approved by the CLSI). The mechanism of resistance identified was FKS1/FKS2 gene mutation. These cases have been associated with poor clinical outcomes. Development of in vitro resistance to caspofungin by Aspergillus species have been identified. In limited clinical experience, resistance to caspofungin in patients with invasive aspergillosis has been observed. The mechanism of resistance has not been established. The incidence of resistance to caspofungin by various clinical isolates of Candida and Aspergillus is rare.

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 info tissues peaked at 15 to 2 days after dosing when 92% of the close was recovered to 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 distribution equilibrium and a true estimate of the volume of distribution of caspofungin is currently impossible to obtain.

Biotransformation

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, 206, 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

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 close was recovered during 27 days: 41% in urine and 34% in faeces. There is little excretion or biotransformation of caspofungin during the first 3 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.

Incompatibilities

Do not mix with diluents containing glucose, as caspofungin is not stable in diluents containing glucose. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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 injection.

Diluted 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. Caspofungin (Ascanex) contains no preservations. 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.

Special precautions for storage

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

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

INSTRUCTIONS FOR USE IN ADULT PATIENTS

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 injection. The concentrations of the reconstituted vials will be: 5.2 mg/ml (50 mg vial) or 7.2 mg/ml (70 mg vial).

The white to off-white compact lyophilized powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discoloration. 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

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE	Volume of reconstituted caspofungin (for transfer to intravenous bag or bottle)	Standard preparation (reconstituted caspofungin added to 250)	Reduced volume Infusion (reconstituted caspofungin added to 100)
50 mg	10mL	0.20mg/mL	—
50 mg at reduced volume	10mL	—	0.47 mg/mL
35mg for moderate hepatic impairment (from one 50mg vial)	7mL	0.14 mg/mL	—
35 mg for moderate hepatic impairment (from one 50 mg vial) at reduced volume	7mL	—	0.34 mg/mL

INSTRUCTIONS FOR USE IN PAEDIATRIC

Calculation of Body Surface Area (BSA) for paediatric dosing

Before preparation on infusion, calculate the body surface area (BSA) of the patient using the following formula: (Mosteller Formula)

BSA (m²)= $\sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$

Preparation of the 70mg/m2 infusion for paediatric patients >3 months of age (using a 50-mg vial or a 70-mg vial)

1.

Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
BSA (m2) X 70 mg/m2 = Loading Dose

The maximum loading dose of Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2.

Equilibrate the refrigerated vial of CANCIDAS to room temperature.
3.

Aseptically add 10.5 ml of water for injection. a. This reconstituted solution may be stored for up to 24 hours at or below 25°C.

b. This will give a final caspofungin concentration in the vial of 5.2 mg/ml (if using a 50-mg vial) or 7.2 mg/ml (if using a 70-mg vial).
4.

Remove the volume of medicinal product equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL) of reconstituted CANCIDAS to an IV bag (or bottle) containing 250 ml of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (mL) of reconstituted CANCIDAS can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/mL. 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

Preparation of the 50 mg/m2 infusion for paediatric patients >3 months of age using a 50-mg vial or a 70-mg vial)

1.

Determine the actual daily maintenance dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
BSA (m2) x 50 mg/m2 = Daily Maintenance Dose

The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
2.

Equilibrate the refrigerated vial of caspofungin to room temperature.
3.

Aseptically add 10.5 ml of water for injection. a. This reconstituted solution may be stored for up to 24 hours at or below 25°C. b. This will give a final caspofungin concentration in the vial of 5.2 mg/ml (if using a 50-mg vial) or 7.2 mg/ml (if using a 70-mg vial).
4.

Remove the volume of medicinal product equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (mL) of reconstituted caspofungin to an IV bag (or bottle) containing 250 ml of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (mL) of reconstituted caspofungin can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/mL. 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.

Preparation notes:

- a.

The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.
- b.

Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.
- c.

CANCIDAS is formulated to provide the full labeled vial dose (50 mg or 70 mg) when 10 ml is withdrawn from the vial.

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without a prescription.

STORAGE CONDITIONS:

Store at temperatures between 2° and 8°C. Do not freeze.

AVAILABILITY

50mg Lyophilized Powder for Solution for Infusion in 10mL USP Type I clear glass Iyo vial with 20 mm Bromobutyl rubber stopper and 20 mm aluminum flip-off seals.

ADR Reporting Statement:

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph and BIOCare: pv@biocarelifesciences.com
Seek medical attention immediately at the first sign of any adverse drug reaction.

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