For the use only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

PERGILAS

(Caspofungin 50/70 mg Powder for concentrate for solution for infusion)

COMPOSITION

PERGILAS
Each vial contains
Caspofungin Acetate 55.52 mg equivalent to Caspofungin 50 mg
Caspofungin Acetate 77.69 mg equivalent to Caspofungin 70 mg
After reconstitution in 10.5 ml of water for injection, 1 ml of the concentrate contains 5.2 mg or 7.2 mg caspofungin.

Excipients: Sucrose, mannitol, glacial acetic acid, sodium hydroxide, water for injection

PRODUCT DESCRIPTION

Transparent glass vial, bearing grey rubber stopper and aluminum band with plastic flip-off cap, containing white to off white lyophilised powder.
Description after reconstitution/ Dilution of the product: Colorless solution, free from visible particles

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics

Mechanism of Action

Caspofungin acetate, the active ingredient of PERGILAS, inhibits the synthesis of β (1,3)-D-glucan, an essential component of the cell wall of many filamentous fungi and yeast. B (1,3)-D-glucan is not present in mammalian cells.

Activity in vitro

Caspofungin has *in vitro* activity against *Aspergillus* species (including *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus*, and *Aspergillus candidus*) and *Candida* species (including *Candida albicans, Candida dubliniensis, Candida glabrata, Candida guilliermondii, Candida kefyr, Candida krusei, Candida lipolytica, Candida lusitaniae, Candida parapsilosis, Candida rugosa*, and *Candida tropicalis*).

Activity in vivo

Caspofungin has been reported to be active when parenterally administered to immune-competent and immune-suppressed animals with disseminated infections of *Aspergillus* and *Candida* for which the endpoints were prolonged survival of infected animals (*Aspergillus* and *Candida*) and clearance of fungi from target organs (*Candida*). Caspofungin has also been reported to be active in immunodeficient animals after disseminated infection with *C. glabrata, C. krusei, C. lusitaniae, C. parapsilosis*, or *C. tropicalis* in which the endpoint was clearance of *Candida* from target organs. Caspofungin has been reported to be highly active in the prevention and treatment of pulmonary aspergillosis.

Cross-resistance

Caspofungin acetate is active against strains of *Candida* with intrinsic or acquired resistance to fluconazole, amphotericin B, or flucytosine consistent with their different mechanisms of action.

Drug Resistance

Isolates of *Candida* with reduced susceptibility to caspofungin have been reported in a small number of patients during treatment (MICs for caspofungin >2 µg/mL using standardized MIC testing techniques approved by the CLSI). Some of these isolates had mutations in the FKS1/FKS2 gene. Although the incidence is rare, these cases have been routinely reported to be associated with poor clinical outcomes.

Development of *in vitro* resistance to caspofungin in *Aspergillus* species has been reported. In clinical experience, drug resistance in patients with invasive aspergillosis has been reported. The mechanism of resistance has not been established.

The incidence of drug resistance in various clinical isolates of *Candida* and *Aspergillus* species is rare.

Drug Interactions

Caspofungin acetate in combination with amphotericin B, has been reported to have no antagonism of antifungal activity against either *A. fumigatus* or *C. albicans*. Additive/indifferent or synergistic activity against *A. fumigatus* and additive/indifferent activity against *C. albicans* has also been reported. The clinical significance of these results is unknown.

Pharmacokinetics

Absorption

Absorption is not relevant since caspofungin acetate is administered intravenously.

Distribution

Plasma concentrations of caspofungin has been reported to decline in a polyphasic manner following single 1-hour intravenous infusions. A short α -phase occurs immediately post-infusion, followed by a β -

phase with a half-life of 9 to 11 hours that characterizes much of the profile and exhibits clear log-linear behavior from 6 to 48 hours postdose, during which the plasma concentration decreases by 10-fold. An additional γ -phase also occurs with half-life 40-50 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. Caspofungin is extensively bound to albumin (approximately 97%), and distribution into red blood cells is minimal. After a single 70-mg dose of [^{3}H] caspofungin acetate, approximately 92% of the administered radioactivity has been reported to distribute to tissues by 36 to 48 hours. Little excretion or biotransformation of caspofungin has been reported during the first 30 hours after administration.

Metabolism

Caspofungin is slowly metabolized by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound. At later time points (≥ 5 days postdose), there is a low level (≤ 7 picomoles/mg protein, or ≤ 1.3% of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin. Additional metabolism involves hydrolysis into constitutive amino acids and their derivatives, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Elimination

Approximately 75% of the radioactivity has been reported to be recovered: 41% in urine and 34% in feces. Plasma concentrations of radioactivity and of caspofungin have been reported to be similar during the first 24 to 48 hours postdose; thereafter drug levels fell more rapidly. In plasma, caspofungin concentrations has been reported to fell below the limit of quantitation after 6 to 8 days postdose, while radiolabel fell below the limit of quantitation at 22.3 weeks postdose. A small amount of caspofungin has been reported to excrete unchanged in urine (approximately 1.4% of dose). Renal clearance of parent drug has also been reported to be low (approximately 0.15 mL/min).

Characteristics in Patients

Gender

Similar plasma concentration of caspofungin has been reported in healthy men and women on Day 1 following a single 70-mg dose. It has been reported that the caspofungin plasma concentration in some women was elevated approximately 20% relative to men after 13 daily 50-mg doses.

Hepatic Insufficiency

Plasma concentrations of caspofungin after a single 70-mg dose in adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) have been reported to increase by approximately 55% in AUC compared to healthy subjects. Plasma concentrations in adult patients with mild hepatic insufficiency has

been reported to increase modestly (19 to 25% in AUC) on Days 7 and 14 after caspofungin (70 mg on Day 1 followed by 50 mg daily thereafter), relative to healthy subjects.

Renal Insufficiency

Caspofungin pharmacokinetics has been reported to be similar in volunteers with mild renal insufficiency (creatinine clearance 50 to 80 mL/ min) and control subjects after single 70-mg doses. Moderate (creatinine clearance 31 to 49 mL/min), advanced (creatinine clearance 5 to 30mL/min), and end- stage (creatinine clearance <10mL/min and dialysis dependent) renal insufficiency have been reported to moderately increase caspofungin plasma concentrations after single-dose administration (range: 30 to 49% for AUC). However, in patients with invasive aspergillosis who received multiple daily doses of caspofungin 50 mg, no significant effect of mild to advanced renal impairment on caspofungin trough concentrations were reported. No dosage adjustment is necessary for patients with renal insufficiency. Caspofungin is not dialyzable, thus supplementary dosing is not required following haemodialysis.

INDICATIONS

PERGILAS is indicated in adult and paediatric patients (12 months and older) for:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of Invasive Candidiasis, including candidemia.
- Treatment of Esophageal Candidiasis.
- Treatment of Invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e. amphotericin B, lipid formulations of amphotericin B, and/ or itraconazole). Caspofungin has not been studied as initial therapy for invasive aspergillosis.

DOSE AND METHOD OF ADMINISTRATION

General Recommendations in Adult Patients

PERGILAS should be administered in adults (≥ 18 years of age) by slow intravenous infusion over approximately 1 hour.

Empirical Therapy

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. If the 50-mg dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. Although an increase in efficacy with 70 mg daily has not been demonstrated, limited reported safety data suggest that an increase in dose to 70 mg daily is well tolerated.

Invasive Candidiasis

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment of invasive candidiasis should be dictated by the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. Patients who remain persistently neutropenic may warrant a longer course of therapy pending resolution of the neutropenia.

Esophageal Candidiasis

Fifty (50) mg should be administered daily.

Invasive Aspergillosis

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. Although there is no information to demonstrate an increase in efficacy with higher doses, reported safety data suggests that an increase in dose to 70 mg daily may be considered in patients without evidence of clinical response in whom PERGILAS has been well tolerated.

No dosage adjustment is necessary for elderly patients (65 years of age or more).

No dosage adjustment is necessary based on gender, race, or renal impairment.

When co-administering caspofungin in adult patients with the metabolic inducers efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg caspofungin should be considered.

Patients with Hepatic Insufficiency

Adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment. For adult patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), caspofungin 35 mg daily is recommended based upon reported pharmacokinetic data. However, where recommended, a 70-mg loading dose should still be administered on Day 1. There is no clinical experience in adult patients with severe hepatic insufficiency (Child-Pugh score greater than 9) and in paediatric patients with any degree of hepatic insufficiency.

Paediatric Patients

Caspofungin should be administered in paediatric patients (12 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in paediatric patients (12 months to 17 years of age) 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/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). Duration of treatment should be individualized to the indication, as described for each indication in adults (see General Recommendations in Adult Patients).

If the 50-mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg). Although an increase in efficacy with 70 mg/m^2 daily has not been demonstrated, limited reported safety data suggest that an increase in dose to 70 mg/m^2 daily is well tolerated.

When caspofungin is co-administered to paediatric patients with inducers of drug clearance, such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, use of a caspofungin dose of 70-mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

It has been reported that the efficacy and safety of caspofungin have not been sufficiently studied involving neonates and infants below 12 months of age.

Reconstitution of PERGILAS

DO NOT USE ANY DILUENTS CONTAINING DEXTROSE (α -D-GLUCOSE), as PERGILAS is not stable in diluents containing dextrose. DO NOT MIX OR CO-INFUSE PERGILAS WITH ANY OTHER MEDICATIONS, as there is no data available on the compatibility of PERGILAS with other intravenous substances, additives, or medications. Visually inspect the infusion solution for particulate matter or discoloration.

INSTRUCTIONS FOR USE IN ADULTS

Step 1 Reconstitution of vials

To reconstitute the powder, bring the refrigerated vial of PERGILAS to room temperature and aseptically add 10.5 ml of Sterile Water for Injection. The concentrations of the reconstituted vials will be: 7.2 mg/mL (70 mg vial) or 5.2 mg/ml (50 mg vial).

The white to off-white compact 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 PERGILAS to patient infusion solution

Diluents for the final patient infusion solutions are: Sterile Saline for Injection, or Lactated Ringer's Solution. The standard patient infusion is prepared by aseptically adding the appropriate amount of reconstituted drug (as shown in the table below) to a 100 ml intravenous bag or bottle. For a 70 mg dose, withdraw two separate 5 ml aliquots of the reconstituted solution and add one aliquot to each of two separate 100 mL intravenous bags or bottles. Dilution of a 70 mg dose in a single 100 ml intravenous bag or bottle is not recommended. Do not use if the solution is cloudy or 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. PERGILAS should be administered by slow intravenous infusion over approximately 1 hour. For the 70 mg dose, the two intravenous bags or bottles should be infused

sequentially. Each of the bags or bottles should be infused over approximately 30 minutes, for a total infusion time of approximately one hour.

PREPARATION OF THE PATIENT INFUSION SOLUTIONS IN ADULTS

DOSE*	Volume of reconstituted PERGILAS for transfer to intravenous bag or bottle	Typical preparation (reconstituted PERGILAS added to 100 mL) final concentration
70 mg (from one 70 mg vial) (Dilute in two bags of 100 mL)**	5 mL in each 100 mL IV bag or bottle	0.33 mg/mL
50 mg (from one 50 mg vial)	10 mL	0.45 mg/mL
35 mg for moderate hepatic insufficiency (from one 70 mg vial)	5 mL	0.33 mg/mL
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 mL	0.33 mg/mL
* 10.5 mL should be used for reconstitution of all vials ** Dilute 5 mL of the reconstituted vial in a 100mL IV bag/bottle and the other 5 mL in a second 100mL IV bag/bottle.		

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric dosing

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

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

Preparation of the 70 mg/m² infusion for paediatric patients 12 months of age or older (using 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 (m^2) X 70 mg/m^2 = Loading Dose
   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Equilibrate the refrigerated vial of PERGILAS to room temperature.
3. Aseptically add 10.5 ml of Sterile 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 7.2 mg/ml.
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted PERGILAS 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)[c] of reconstituted PERGILAS 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.

5. If the calculated loading dose is <50 mg, then the dose may be prepared from the 50-mg vial [follow Steps 2-4 from Preparation of the 50 mg/m^2 infusion for pediatric patients 12 months of age or older (using a 50-mg vial)]. The final caspofungin concentration in the 50-mg vial after reconstitution is 5.2 mg/ml.

Preparation of the 50 mg/m^2 infusion for paediatric patients 12 months of age or older (using a 50-mg vial)

1. Determine the daily maintenance dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:
   BSA (m^2) X 50 mg/m^2 = 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 PERGILAS to room temperature.
3. Aseptically add 10.5 ml of Sterile 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.
4. Remove the volume of medicinal product equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (ml) [c] of reconstituted [PERGILAS] 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) [c] of reconstituted [PERGILAS] 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
5. If the actual daily maintenance dose is >50 mg, then the dose may be prepared from the 70-mg vial [follow Steps 2-4 from Preparation of the 70 mg/m^2 infusion for pediatric patients 12 months of age or older (using a 70-mg vial)]. The final caspofungin concentration in the 70-mg vial after reconstitution is 7.2 mg/mL.

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 discolouration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

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

Route of administration: Parenteral Use (intravenous infusion)

CONTRAINDICATIONS

PERGILAS is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients of this product.

WARNINGS AND PRECAUTIONS

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 bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment.

Limited data report 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 caspofungin with ciclosporin has been reported in healthy adult volunteers and in adult patients. Some healthy adult volunteers who received two 3 mg/kg doses of ciclosporin with caspofungin reported 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. An increase of approximately 35% in the area under the curve (AUC) of caspofungin has been reported when caspofungin and ciclosporin were co-administered; blood levels of ciclosporin remained unchanged. In patients treated with caspofungin and ciclosporin for 1 to 290 days (median 17.5 days), no serious hepatic adverse reactions have been reported. In patients with allogeneic haematopoietic stem cell transplants or solid organ transplants, hepatic enzyme abnormalities have been reported commonly; however, no patients had elevations in ALT that were considered drug related. Elevations in AST considered at least possibly related to therapy with caspofungin and/or ciclosporin have been reported in few patients, but all were less than 3.6 times the ULN. Discontinuation due to laboratory abnormalities in hepatic enzymes from any cause have been reported in patients; few were considered possibly related to therapy with caspofungin and/or ciclosporin as well as other possible causes. In adult patients treated with caspofungin and ciclosporin for 2 to 56 days; no increase in hepatic enzymes has been reported. These reported 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 has been reported to increase 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 (see DOSE AND METHOD OF ADMINISTRATION and PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES).

Laboratory abnormalities in liver function tests have been reported 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.

Cases of Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post-marketing use of caspofungin. Caution should apply in patients with history of allergic skin reaction (see SIDE EFFECTS/ ADVERSE REACTIONS).

Paediatric use

The safety and effectiveness of caspofungin in paediatric patients 12 months to 17 years of age has been adequately reported for the following indications (see INDICATIONS):

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients
- Treatment of invasive candidiasis, including candidemia
- Treatment of esophageal candidiasis
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e. amphotericin B, lipid formulations of amphotericin B, and/or itraconazole)

The efficacy and safety of caspofungin have not been adequately reported in neonates and infants under 3 months of age.

The use of Caspofungin has not been reported in paediatric patients with endocarditis, osteomyelitis, and meningitis due to *Candida*. Caspofungin use has also not been reported as initial therapy for invasive aspergillosis in paediatric patients.

Geriatric use

The plasma concentration of caspofungin in healthy older men and women (65 years of age or more) has been reported to increase slightly (approximately 28% in AUC) compared to young healthy males. In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was reported in older patients relative to younger patients. No dosage adjustment is necessary for elderly patients (65 years of age or more).

Warning for excipients

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

General

The efficacy of a 70-mg dose regimen in patients with invasive aspergillosis who are not clinically responding to the 50 mg daily dose is not known. An increase in dose to 70 mg daily has been reported to be well tolerated. The safety and efficacy of doses above 70 mg have not been adequately reported.

The safety information on treatment durations longer than 2 weeks is limited; however, reported data suggest that caspofungin continues to be well tolerated with longer courses of therapy.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

None reported.

Effects on ability to drive and use machines

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

DRUG INTERACTIONS

Caspofungin is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. 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 reported to interact with other medicinal products (see below).

Ciclosporin A (one 4 mg/kg dose or two 3 mg/kg doses 12 hours apart) has been reported to increase the AUC of caspofungin by approximately 35 % in healthy adult subjects. These AUC increases are probably due to reduced uptake of caspofungin by the liver. Caspofungin did not increase the plasma levels of ciclosporin. Transient increases in liver ALT and AST of less than or equal to 3-fold the upper limit of normal (ULN) has been reported when caspofungin and ciclosporin were co-administered, that resolved with discontinuation of the medicinal products. No serious hepatic adverse reactions have been reported in patients treated with caspofungin and ciclosporin for 1 to 290 days (median 17.5 days) (see WARNINGS AND PRECAUTIONS). Close monitoring of liver enzymes should be considered if the two medicinal products are used concomitantly. Caspofungin has been reported to reduce 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.

The pharmacokinetics of caspofungin have been reported to be not altered to a clinically relevant extent by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus in healthy adult volunteers. Caspofungin has also reported to not influence the pharmacokinetics of amphotericin B, itraconazole, rifampicin or mycophenolate mofetil. No special precautions are needed when amphotericin B, itraconazole, nelfinavir or mycophenolate mofetil are co-administered with caspofungin.

Rifampicin has been reported to cause 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. 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 (see DOSE AND METHOD OF ADMINISTRATION).

The interaction of caspofungin doses higher than 50 or 70 mg daily with other medicinal products has not been formally reported.

In paediatric patients, 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 reported 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/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

SIDE EFFECTS/ ADVERSE REACTIONS

Hypersensitivity reactions (anaphylaxis and possibly histamine-mediated adverse reactions) have been reported (see WARNINGS AND PRECAUTIONS).

Pulmonary oedema, adult respiratory distress syndrome (ARDS), and radiographic infiltrates has been reported in patients with invasive aspergillosis.

Adult patients

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 adults treated with caspofungin were typically mild and rarely led to discontinuation.

Tabulated list of adverse reactions

The following adverse reactions were reported:

System Organ Class	*Common*	*Uncommon*	*Not known (cannot be estimated from reported data)*
Blood and lymphatic system disorders	haemoglobin decreased, haematocrit decreased, white blood cell count decreased	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	Hypokalemia	fluid overload, hypomagnesaemia, anorexia, electrolyte imbalance, hyperglycaemia, hypocalcaemia,	

		metabolic acidosis	
Psychiatric disorders		anxiety, disorientation, insomnia	
Nervous system disorders	headache	dizziness, dysgeusia, paraesthesia, somnolence, tremor, hypoaesthesia	
Eye disorders		ocular icterus, vision blurred, eyelid oedema, lacrimation increased	
Cardiac disorders		palpitations, tachycardia, arrhythmia, atrial fibrillation, cardiac failure congestive	
Vascular disorders	phlebitis	thrombophlebitis, flushing, hot flush, hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders	dyspnoea	nasal congestion, pharyngolaryngeal pain, tachypnoea, bronchospasm, cough, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing	
Gastrointestinal disorders	nausea, diarrhoea, vomiting	abdominal pain, abdominal pain upper, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia, flatulence	
Hepatobiliary disorders	elevated liver values (alanine aminotransferase, aspartate aminotranserase, blood alkaline phosphatase, bilirubin conjugated, blood bilirubin)	cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, hepatic function abnormal, hepatotoxicity, liver disorder, gamma-glutamyltransferase increased	
Skin and subcutaneous tissue disorders	rash, pruritus, erythema, hyperhidrosis	erythema multiforme, rash macular, rash maculo-papular, rash pruritic, urticaria, dermatitis allergic, pruritus generalised, rash erythematous, rash generalised, rash morbilliform, skin lesion	Toxic epidermal necrolysis and Stevens-Johnson syndrome (see WARNINGS AND PRECAUTIONS)
Musculoskeletal and connective tissue disorders	arthralgia	back pain, pain in extremity, bone pain, muscular weakness, myalgia	
Renal and urinary disorders		renal failure, renal failure acute	
General disorders and administration site conditions	pyrexia, chills, infusion-site pruritus	pain, catheter site pain, fatigue, feeling cold, feeling hot, infusion site erythema, infusion site induration, infusion site pain, infusion site swelling, injection site phlebitis, oedema peripheral, tenderness, chest discomfort, chest pain, face oedema, feeling of body temperature change, induration, infusion site extravasation, infusion site irritation, infusion site phlebitis, infusion site rash, infusion site urticaria, injection site erythema, injection site oedema, injection site pain, injection site swelling, malaise, oedema	

Investigations	blood potassium decreased, blood albumin decreased	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.	

The safety of caspofungin 150 mg daily (for up to 51 days) has been reported to be generally similar to patients receiving the 50-mg daily dose of caspofungin. The proportion of patients with a serious drug-related adverse reaction or a drug-related adverse reaction leading to caspofungin discontinuation was reported to be comparable in the 2 treatment groups.

Paediatric Patients

The overall incidence of clinical adverse experiences reported in paediatric patients 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, rash and headache.

Reported drug-related clinical and laboratory abnormalities among all paediatric patients treated with caspofungin were typically mild and rarely led to discontinuation.

Tabulated list of adverse reactions

The following adverse reactions were reported:

System Organ Class	*Very common*	*Common*
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	fever	chills, catheter site pain
Investigations		decreased potassium, hypomagnesemia, increased glucose, decreased phosphorus, and increased phosphorus

Pregnancy

There are no or limited data reported from the use of caspofungin in pregnant women. Caspofungin should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether caspofungin is excreted in human milk. Women receiving caspofungin should not breast-feed.

Fertility

There are no clinical data reported for caspofungin to assess its impact on fertility.

OVERDOSE

A single dose of 210 mg to adult healthy subjects, has been reported to be generally well tolerated. In addition, 100 mg once daily for 21 days administered to adult healthy subjects has been reported to be generally well tolerated. 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.

INCOMPATIBILITIES

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

STORAGE

Storage of Unopened vial:

The lyophilized compact powder in vials should be stored at 2 to 8°C.

Storage of reconstituted PERGILAS in vials:

Reconstituted PERGILAS may be stored at or below 25°C for up to 24 hours prior to the preparation of the patient infusion solution.

Storage of diluted product for infusion:

The final patient infusion solution in the intravenous bag or bottle can be stored at or below 25°C for up to 24 hours, or for up to 48 hours when refrigerated at 2 to 8°C.

PERGILAS contains no preservatives. From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination 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.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

SUPPLY: 50 mg/vial; 70 mg/vial
Dosage Form: Powder for concentrate for solution for infusion
Packaging: Glass vial type I, sealed with rubber stopper and aluminium band with plastic flip-off cap
Pack Size: Supplied in packs of 1 vial

Date of Revision: January 2021

Manufactured by:
Main manufacturer (contract site)
MEFAR ILAC; SANAYII A.S.,
Ramazanoglu Mah. Ensar Cad.
No.20, 34906,
Kurtkoy-Pendik- Istanbul,
Turkey
Batch releaser
PHARMATHEN S.A.
Dervenakion 6, Pallini - 15351,
Attikis Greece
Product Owner:
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