

CASPOFUNGIN ACETATE FOR INJECTION 50 mg (Lyophilized)
CASPOFUNGIN ACETATE FOR INJECTION 70 mg (Lyophilized)
CASPERCID®

COMPOSITION

CASPERCID® 50

CASPOFUNGIN ACETATE FOR INJECTION 50 mg (Lyophilized)

Each vial contains

Caspofungin Acetate

Equivalent to Caspofungin 50 mg

Excipients q.s.

One Ampoule containing sterile water for Injection IP

CASPERCID® 70

CASPOFUNGIN ACETATE FOR INJECTION 70 mg (Lyophilized)

Each vial contains

Caspofungin Acetate

Equivalent to Caspofungin 70 mg

Excipients q.s.

One Ampoule containing sterile water for Injection IP

INDICATION

CASPERCID® is indicated in adults and paediatric patients (3 months and older) for the following:

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of candidaemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections.
- Treatment of oesophageal 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, itraconazole).

It has not been studied in endocarditis, osteomyelitis and meningitis due to *Candida* and as initial therapy for invasive aspergillosis.

DOSAGE AND ADMINISTRATION

DOSAGE

CASPERCID® should be administered by slow I.V. infusion over approximately 1 hour. CASPERCID® should not be administered by I.V. bolus administration.

Adults (18 years of age or older)

Empirical Therapy for presumed fungal Infections in Febrile & Neutropenic patients

Administer a single 70-mg loading dose on Day 1, followed by 50 mg once daily thereafter. Duration of treatment should be based on the patient's clinical response. Continue empirical therapy until resolution of neutropenia. In general, treat patients found to have a fungal infection for a minimum of 14 days after the last positive culture and continue treatment 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.

Candidemia and Other Candida Infections

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

Oesophageal Candidiasis

The dose is 50 mg once daily for 7 to 14 days after symptom resolution. A 70-mg loading dose has not been studied for this indication. Because of the risk of relapse of oropharyngeal candidiasis in patients with HIV infections, suppressive oral therapy could be considered.

Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies

Administer a single 70-mg loading dose on Day 1, followed by 50 mg once daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

Paediatric Patients (3 months to 17 years of age).

For all indications, administer a single 70 mg/m² loading dose on Day 1, followed by 50 mg/m² once daily thereafter. The maximum loading dose and the daily maintenance dose should not exceed 70mg, regardless of the patient's calculated dose. Dosing in pediatric patients (3 months to 17 years of age) should be based on the patient's body surface area (BSA) as calculated by the Mosteller Formula.

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

Following calculation of the patient's BSA, the loading dose in milligrams should be calculated as BSA (m²) X 70 mg/m². The maintenance dose in milligrams should be calculated as BSA (m²) X 50 mg/m². Duration of treatment should be individualized to the indication, as described for each indication in adults. If the 50-mg/m² daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m² daily (not to exceed 70 mg).

Dosage Adjustments in Patients with Hepatic Impairment

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

Dosage Adjustments in Patients Receiving Concomitant Inducers of Hepatic CYP Enzymes

Adult Patients:

Adult patients on rifampin should receive 70 mg of caspofungin once daily. When caspofungin is coadministered to adult patients with other inducers of hepatic CYP enzymes such as nevirapine, efavirenz, carbamazepine, dexamethasone, or phenytoin, administration of a daily dose of 70 mg of caspofungin should be considered.

Pediatric Patients:

Pediatric patients on rifampin should receive 70 mg/m² of caspofungin daily (not to exceed an actual daily dose of 70 mg). When caspofungin is co-administered to pediatric patients with other inducers of hepatic CYP enzymes, such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a caspofungin dose of 70 mg/m² once daily (not to exceed 70 mg) should be considered.

METHOD OF ADMINISTRATION

Administer by slow I.V. infusion over approximately 1 hour. Not for I.V. bolus administration.

DO NOT USE ANY DILUENTS CONTAINING DEXTROSE (α -D-GLUCOSE). Do not mix or co-infuse CASPERCID® with other medications. Visually inspect the infusion solution for particulate matter or discoloration.

Step 1: Equilibrate the refrigerated vial of CASPERCID® to room temperature.

Step 2: Reconstitution : Aseptically add 10 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection along with methylparaben and propylparaben, or Bacteriostatic Water for Injection along with 0.9% benzyl alcohol to the vial.

Step 3: The volume of diluent to be added to each vial and the drug concentration of the resulting solution is listed in Table 1 below.

Table 1: Information for the preparation of CASPERCID® I.V

CASPERCID® vial	Volume of diluent to be added*	Resulting concentration following reconstitution
70 mg	10 mL	7 mg/mL
50 mg	10 mL	5 mg/mL

Mix gently until a clear solution is obtained. 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.

CASPERCID® vials are for single use only; the remaining solution should be discarded.

However, the reconstituted solution may be stored for up to 24 hours at $\leq 25^{\circ}\text{C}$ ($\leq 77^{\circ}\text{F}$) prior to preparation of the infusion solution for the patient.

Step 3: Preparation of the infusion solution for the patient

- I. Aseptically transfer the appropriate volume (mL) of reconstituted CASPERCID® to an I.V. bag (or bottle) containing 250 mL of 0.9%, 0.45% or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection.
- II. Alternatively, reduced volume infusions in 100 ml may be used, where medically necessary, for 50 mg or 35 mg daily doses.
- III. Do not use if the solution is cloudy or has precipitated.
- IV. This infusion solution must be used within 24 hours if stored at $\leq 25^{\circ}\text{C}$, or within 48 hours if stored refrigerated at 2-8°C.

Dose	Volume of reconstituted CASPERCID® for transfer to I.V. bag or bottle	Typical preparation (reconstituted CASPERCID® added to 250 mL) final concentration	Reduced volume infusion (reconstituted CASPERCID® injection added to 100 mL) final concentration
70 mg	10 mL	0.28 mg/mL	Not recommended
70 mg (from two 50 mg vials)*	14 mL	0.28 mg/mL	Not recommended
50 mg	10 mL	0.20 mg/mL	0.5 mg/mL
35 mg for moderate	5 mL	0.14 mg/mL	0.35 mg/mL

hepatic impairment (from one 70 mg vial)			
35 mg for moderate hepatic impairment (from one 50 mg vial)	7 mL	0.14 mg/mL	0.35 mg/mL

**If a 70 mg vial is not available, the 70 mg dose can be prepared from two 50 mg vials.*

Special Considerations for Paediatric Patients (3 Months of Age or Older)

Before preparation of the infusion, calculate the BSA of the patient using the Mosteller Formula:

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

Preparation of the 70 mg/m² infusion for paediatric patients, 3 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: $BSA (m^2) \times 70 \text{ mg/m}^2 = \text{Loading dose}$.

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 CASPERCID® to room temperature.
3. Aseptically add 10 ml of 0.9 % Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben. This reconstituted solution may be stored for up to 1 hour at 7 mg/ml (if using a 70 mg vial).
4. Remove the volume of drug equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml) of reconstituted CASPERCID® to an I.V. bag (or bottle) containing 250 ml of 0.9%, 0.45% or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection. Alternatively, the volume (ml) of reconstituted CASPERCID® can be added to a reduced volume of 0.9%, 0.45% or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at $\leq 25^\circ\text{C}$ ($\leq 77^\circ\text{F}$) or within 48 hours if stored refrigerated at $2-8^\circ\text{C}$ ($36-46^\circ\text{F}$).
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/m² infusion for paediatric patients, 3 months of age or older, (using a 50 mg vial)}.

Preparation of the 50 mg/m² infusion for pediatric patients, 3 months of age or older (using a 50 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:
2. $BSA (m^2) \times 50 \text{ mg/m}^2 = \text{Daily maintenance dose}$
3. The daily maintenance dose should not exceed 70 mg regardless of the patient's calculated dose.
4. Equilibrate the refrigerated vial of CASPERCID® to room temperature.
5. Aseptically add 10 ml of 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben. This reconstituted solution may be stored for up to 1

hour at $\leq 25^{\circ}\text{C}$ ($\leq 77^{\circ}\text{F}$). This will give a final caspofungin concentration in the vial of 5 mg/ml (if using a 50 mg vial).

6. Remove the volume of drug equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (ml) of reconstituted CASPERCID® to an I.V. bag (or bottle) containing 250 ml of 0.9%, 0.45% or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection. Alternatively, the volume (ml) of reconstituted CASPERCID® can be added to a reduced volume of 0.9%, 0.45% or 0.225% Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0.5 mg/ml. This infusion solution must be used within 24 hours if stored at $\leq 25^{\circ}\text{C}$ ($\leq 77^{\circ}\text{F}$) or within 48 hours if stored refrigerated at $2-8^{\circ}\text{C}$ ($36-46^{\circ}\text{F}$).
7. If the calculated 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/m² infusion for paediatric patients, 3 months of age or older, (using a 70 mg vial)}.

INCOMPATIBILITIES

Do not mix or co-infuse CASPERCID® with other medications. **DO NOT USE DILUENTS CONTAINING DEXTROSE (-D-GLUCOSE).**

STORAGE AND HANDLING INSTRUCTIONS

Before opening:

The lyophilized vials should be stored refrigerated at $2-8^{\circ}\text{C}$ ($36-46^{\circ}\text{F}$).

Reconstituted solutions:

It is recommended that the reconstituted solutions be used immediately. However, the reconstitutes may be stored at $\leq 25^{\circ}\text{C}$ ($\leq 77^{\circ}\text{F}$) for 24 hours prior to the preparation of the infusion solutions for the patients.

Diluted solutions:

It is recommended to use the reconstituted solution immediately; however, the final infusion solution for the patient in the I.V. bag or bottle can be stored at $^{\circ}\text{C}$ ($^{\circ}\text{F}$) for up to 24 hours, or up to 48 hours when refrigerated at $2-8^{\circ}\text{C}$.

CONTRAINDICATION

CASPERCID® is contraindicated in patients with known hypersensitivity to any component of this product.

WARNINGS AND PRECAUTIONS

General

Hypersensitivity:

Anaphylaxis has been reported during administration of caspofungin. If this occurs, caspofungin should be discontinued and appropriate treatment administered. Possible histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, bronchospasm and cases of Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported and may require discontinuation and/or administration of appropriate treatment.

Concomitant Use with Cyclosporine :

Elevated liver enzymes have occurred in patients receiving caspofungin and cyclosporine concomitantly. Only use CASPERCID® and cyclosporine in those patients for whom the potential benefit outweighs the potential risk.

Patients who develop abnormal liver enzymes during concomitant therapy should be monitored and risk / benefit of continuing therapy should be evaluated.

Hepatic Effects

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

DRUG INTERACTIONS

Studies *in vitro* show that caspofungin acetate is not an inhibitor of any enzyme in the cytochrome (CYP) 450 system. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other drugs. Caspofungin acetate is not a substrate for P-glycoprotein and is a poor substrate for CYP450 enzymes.

Clinical studies in adult healthy volunteers show that the pharmacokinetics of caspofungin acetate is not altered by itraconazole, amphotericin B, mycophenolate, nelfinavir or tacrolimus. Caspofungin acetate has no effect on the pharmacokinetics of itraconazole, amphotericin B or the active metabolite of mycophenolate.

Cyclosporine

There were transient increases in liver ALT and AST when caspofungin acetate and cyclosporine were co-administered. Monitor patients who develop abnormal liver enzymes during concomitant therapy and evaluate the risk/benefit of continuing therapy.

Tacrolimus

For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended.

Inducers of Hepatic CYP Enzymes

Rifampin

A drug-drug interaction study with rifampin in healthy adult volunteers has shown a 30% decrease in caspofungin trough concentrations. Adult patients on rifampin should receive 70 mg of CASPERCID® daily and pediatric patients on rifampin should receive 70mg/m² of CASPERCID® daily (not to exceed an actual daily dose of 70mg)

Other Inducers of CYP Enzymes

Adults: When CASPERCID® is co-administered to adult patients with inducers of drug clearance, such as efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine, use of a daily dose of 70 mg of CASPERCID® should be considered.

Paediatric patients: When CASPERCID® is co-administered to paediatric patients with inducers of drug clearance, such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine, a CASPERCID® dose of 70 mg/m² daily (not to exceed an actual daily dose of 70 mg) should be considered.

SPECIAL POPULATIONS

RENAL IMPAIRMENT

No dosage adjustment is necessary for patients with renal impairment. Caspofungin is not dialysable; thus, supplementary dosing is not required following haemodialysis.

HEPATIC IMPAIRMENT:

Please refer under DOSAGE AND ADMINISTRATION.

PREGNANCY

There are no adequate and well-controlled studies in pregnant women. In animal studies, caspofungin caused embryofetal toxicity, including increased resorptions, increased peri-implantation loss and incomplete ossification at multiple foetal sites. CASPERCID® should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

In offspring born to pregnant rats treated with caspofungin at doses comparable to the human dose based on body surface area comparisons, there was incomplete ossification of the skull and torso and increased incidences of cervical rib. There was also an increase in resorptions and peri-implantation losses. In pregnant rabbits treated with caspofungin at doses comparable to two times the human dose based on BSA comparisons, there was an increased incidence of incomplete ossification of the talus/calcaneus in the offspring and increases in foetal resorptions. Caspofungin crossed the placenta in rats and rabbits and was detectable in foetal plasma.

LACTATION

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.

PAEDIATRIC USE

Please refer under INDICATIONS and DOSAGE AND ADMINISTRATION.

The safety and effectiveness of caspofungin in paediatric patients 3 months to 17 years of age are supported by evidence from adequate and well controlled studies in adults, pharmacokinetic data in paediatric patients and additional data from prospective studies in paediatric patients 3 months to 17 years of age for the following indications :

- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis, and pleural space infections.
- Treatment of esophageal candidiasis.
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole)

The efficacy and safety of caspofungin acetate has not been adequately studied in prospective clinical trials involving neonates and infants less than 3 months of age. Although limited pharmacokinetic data were collected in neonates and infants less than 3 months of age, these data are insufficient to establish a safe and effective dose of caspofungin acetate in the treatment of neonatal candidiasis. Invasive candidiasis in neonates has a higher rate of central nervous system (CNS) and multi-organ involvement than in older patients; the ability of caspofungin acetate to penetrate the blood-brain barrier and to treat patients with meningitis and endocarditis is unknown.

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

GERIATRIC USE

No dose adjustment is recommended for the elderly; however, the greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adults: Most common adverse reactions (incidence 10% or greater) are diarrhea, pyrexia, ALT/AST increased, blood alkaline phosphatase increased, and blood potassium decreased.

Paediatric patients: Most common adverse reactions (incidence $\geq 10\%$) are pyrexia, diarrhea, rash, ALT/AST increased, blood potassium decreased, hypotension, and chills.

Clinically significant adverse reactions, regardless of causality or incidence which occurred in less than 5% of patients, are listed below:

- **Blood and Lymphatic System Disorders:** Anaemia, coagulopathy, febrile neutropenia, neutropenia, thrombocytopenia
- **Cardiac Disorders:** Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, myocardial infarction, tachycardia
- **Gastrointestinal Disorders:** Abdominal distension, abdominal pain upper, constipation, dyspepsia
- **General Disorders and Administration Site Conditions:** Asthenia, fatigue, infusion site pain/pruritus/swelling, mucosal inflammation, oedema
- **Hepatobiliary Disorders:** Hepatic failure, hepatomegaly, hepatotoxicity, hyperbilirubinaemia, jaundice
- **Infections and Infestations:** Bacteraemia, sepsis, urinary tract infection
- **Metabolic and Nutrition Disorders:** Anorexia, decreased appetite, fluid overload, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypokalaemia
- **Musculoskeletal, Connective Tissue and Bone Disorders:** Arthralgia, back pain, pain in extremity
- **Nervous System Disorders:** Convulsion, dizziness, somnolence, tremor
- **Psychiatric Disorders:** Anxiety, confusional state, depression, insomnia
- **Renal and Urinary Disorders:** Haematuria, renal failure
- **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnoea, epistaxis, hypoxia, tachypnoea
- **Skin and Subcutaneous Tissue Disorders:** Erythema, petechiae, skin lesion, urticaria
- **Vascular Disorders:** Flushing, hypertension, phlebitis

The following additional adverse reactions have been identified during the post-approval use of caspofungin acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- **Gastrointestinal Disorders:** Pancreatitis
- **Hepatobiliary Disorders:** Hepatic necrosis
- **Skin and Subcutaneous Tissue Disorders:** Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin exfoliation
- **Renal and Urinary Disorders:** Clinically significant renal dysfunction
- **General Disorders and Administration Site Conditions:** Swelling and peripheral oedema
- **Laboratory abnormalities:** gamma-glutamyltransferase increased

OVERDOSAGE

In 6 healthy subjects who received a single 210 mg dose, no significant adverse reactions were reported. Multiple doses above 150 mg daily have not been studied. Caspofungin is not dialysable.

In clinical trials, 1 paediatric patient (16 years of age) unintentionally received a single dose of caspofungin of 113 mg (on day 1), followed by 80 mg daily for an additional 7 days. No clinically significant adverse reactions were reported.

PACK PRESENTATION

- 1 Vial of CASPERCID®50 mg + 1 Sterile Water For Injection ampoule
- 1 Vial CASPERCID®70 mg + 1 Sterile Water For Injection ampoule

Manufactured by:

BDR Pharmaceutical International Private Limited

Shivam Complex No. 1, S-11

B/4, Dunetha, Nani Daman-396210

At: M/s Sovereign Pharma Pvt. Ltd., Survey No 46/1-4, Kadaiya Village,

Nani Daman-396 210

Marketed by:

Sanofi India Limited

Sanofi House, CT Survey No 117-B

L&T Business Park, Saki Vihar Road,

Powai, Mumbai-400072

Source:

- Prescribing Information of Caspogin Injection (Cipla) dated October 2013, published Sep 2014.
- US SmPC of Cancidas® (Merck Sharp & Dohme) dated March 2018 (Reference ID: 4233543) accessed on 11th April 2018

Updated: June 2018