Arofungin 50 mg powder for concentrated solution for infusion

Arofungin 70 mg powder for concentrated solution for infusion

1. COMPOSITION

Arofungin 50 mg powder for concentrated solution for infusion:

Each vial contains 50 mg Caspofungin (as acetate).

Arofungin 70 mg powder for concentrated solution for infusion:

Each vial contains 70 mg Caspofungin (as acetate) .

List of excipients: Sucrose, Mannitol, Glacial acetic acid, Sodium hydroxide

2. PHARMACEUTICAL FORM

Powder for concentrated solution for infusion.

White to off white lyophilised powder.

3. THERAPEUTIC CLASS

Echinocandins Antifungals

4. INDICATIONS AND USAGE

CASPOFUNGIN acetate for injection is an echinocandin antifungal indicated in adults and pediatric patients (3 months of age and older) for:

4.1. Empirical therapy for presumed fungal infections in febrile, neutropenic patients

4.2. Treatment of candidemia and the following candida infections: intra-abdominal abscesses, peritonitis, and pleural space infections.

(Limitation of use: CASPOFUNGIN acetate has not been studied in endocarditis, osteomyelitis due to candida.)

4.3. Treatment of esophageal candidiasis.

(Limitation of use: CASPOFUNGIN acetate has not been approved for the treatment of oropharyngeal candidiasis (OPC))

4.4. Treatment of invasive aspergillosis in patient who are refractory to or intolerant of other therapies.

(Limitation of use: CASPOFUNGIN acetate has not been studied as initial therapy for invasive aspergillosis.)

5. CLINICAL PARTICULARS

5.1. Administration Instructions

CASPOFUNGIN acetate should be initiated by a physician experienced in the management of invasive fungal infection.

After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour. Do not mix or co-infuse CASPOFUNGIN acetate with the other medicines, as there are no data available on the compatibility of CASPOFUNGIN acetate with other intravenous substances, additives, or medications. DO NOT DILUTE THE

CASPOFUNGIN acetate WITH DILUENTS CONTAING GLUCOSE (α-D-glucose), as CASPOFUNGIN acetate is not stable in diluents containing dextrose.

5.2. Therapeutical indications and dosage

5.2.1. Dosing in adult Patients [18 years of age and older]

Empirical therapy for Presumed Fungal Infection 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` 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 neutropenia.

Esophageal 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 infection, suppressive oral therapy could be considered.

Invasive Aspergillosis:

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` underlying disease, recovery from immunosuppression, and clinical response.

5.2.2. Dosing in Pediatric Patients [3 months to 17 years of age]

For all indications, administer a single 70 mg/m^2 loading dose on Day 1, followed by 50 mg/m^2 once daily thereafter. **The maximum loading dose and the daily maintenance dose should not exceed 70 mg, regardless of the patent`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:

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

Following calculation of the patient`s BSA, the loading dose in milligrams should be calculated as BSA (m) × 70 mg/m^2. The maintenance dose in milligrams should be calculated as BAS (m) × 50 mg/m^2.

Duration of treatment should be individualized to the indication, as described for each indication in adults. 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 70 mg)

5.2.3 Dosing 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), acetate 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.

5.2.4 Dosing adjustments in Patients Receiving Concomitant Inducers of Hepatic CYP Enzymes

Adult Patients:

Adult patients on rifampin should receive 70 mg of CASPOFUNGIN acetate once daily. When CASPOFUNGIN acetate is co-administered 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 acetate should be considered.

Pediatric Patients:

Pediatric patients on Rifampin should receive 70 mg/m^2 of CASPOFUNGIN acetate daily (not to exceed an actual daily dose of 70 mg). when CASPOFUNGIN acetate is co-administered to pediatric patients with other inducers of hepatic CYP enzymes, such as Efavirenz, Nevirapine, Phenytoin, Dexamethasone, or Carbamazepine, a CASPOFUNGIN acetate dose of 70 mg/m^2 once daily (not to exceed 70 mg) should be considered.

6. **Preparation for Administration Reconstitution of CASPOFUNGIN acetate for Intravenous Infusion:**
    - Allow the refrigerated vial of CASPOFUNGIN acetate to reach room temperature.
    - Aseptically add 10.5 mL OF 0.9% Sodium Chloride Injection or Sterile Water for Injection, to the vial.
    - Each vial of CASPOFUNGIN acetate contains an intentional overfill of CASPOFUNGIN acetate. Thus, the drug concentration of the resulting is listed in Table 1 below.

Table 1: Information for preparation of CASPOFUNGIN acetate

CASPOFUNGIN acetate vial	Total content (including overfill)	Reconstitution Volume to be added	Resulting concentration following Reconstitution
50 mg	54.6 mg	10.5 mL	5.2 mg/mL
70 mg	75.6 mg	10.5 mL	7.2 mg/mL

- The white to off-white cake will dissolve completely. 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.
- The reconstituted solution of CASPOFUNGIN acetate in the vial should immediately be diluted in the intravenous bag or bottle for infusion.
- CASPOFUNGIN acetate vials are for single use only. Discard unused portion.

Dilution of the Reconstituted Solution in the intravenous Bag for infusion:

- Aseptically transfer the appropriate volume (mL) of reconstituted CASPOFUNGIN acetate to an intravenous (IV) bag (or bottle) containing 250 mL of 0.9% or 0.45%, sodium chloride injection or Lactated Ringers injection.
- Alternatively, the volume (mL) of reconstituted CASPOFUNGIN acetate can be added to a reduce, not to exceed a final concentration of 0.5 mg/mL.
- This diluted infusion solution in the intravenous bag or bottle must be administered immediately after preparation because of microbiological concerns. If it is not used immediately, the person giving the product shall be responsible for the time of storage during usage of the product, and condition of its storage before being used.

  Important Reconstitution and Dilution instructions for pediatric patients 3 Months of Age and Older:

  Follow the reconstitution procedures described above using either the 70-mg or 50-mg vial to create the reconstituted solution. From the reconstituted solution in the vial, remove the volume of drug equal to the calculated loading dose or calculated maintenance dose based on a concentration of 7.2 mg/mL (if reconstituted from the 70-mg vial) or a concentration of 5.2 mg/mL (if reconstituted from the 50-mg vial).

  The choice of vial should be based on total milligram dose of drug to be administered to the pediatric patient. To help ensure accurate dosing, it is recommended for pediatric doses less than 50 mg that 50-mg vials (with a concentration of 5.2 mg/mL) be reserved for pediatric patients requiring doses greater than 50 mg.

  The maximum loading dose and the daily maintenance dose should not exceed 70 mg, regardless of the patient`s calculated dose.

7. CONTRAINDICATIONS

CASPOFUNGIN acetate is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.

8. WARNINGS AND PRECAUTIONS

8.1. Hypersensitivity

Anaphylaxis has been reported during administration of CASPOFUNGIN acetate. If this occurs, discontinue CASPOFUNGIN acetate and administer appropriate treatment. Possible 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.

8.2. Hepatic effects

Use with caution in patients with hepatic impairment; increased transaminases and rare cases of liver impairment (including failure and hepatitis) have been reported in pediatric and adult patients. Monitor liver function tests during therapy; if tests become abnormal or worsen, consider in adults with moderate hepatic impairment (Child-Pugh class B); safety and efficacy have not been established in children with any degree of hepatic impairment (Child – Pugh class C).

8.3. Elevated Liver Enzymes During Concomitant Us with Cyclosporine

Elevated liver enzymes have occurred in patients receiving CASPOFUNGIN acetate and Cyclosporine concomitantly. Only use CASPOFUNGIN acetate 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 the risk/benefit of continuing therapy should be evaluated.

9. ADVERSE REACTIONS

Adverse reaction and incidences reported are associated with monotherapy.

>10%:

Cardiovascular: Hypotension (3% to 20%), peripheral edema (6% to 11%), tachycardia (4% to 11%)

Central nervous system: Fever (6% to 30%), chills (9% to 23%), headache (5% to 15%)

Dermatologic: Rash (4% to 23%)

Endocrine & metabolic: Hypokalemia (5% to 23%)

Gastrointestinal: Diarrhea (6% to 27%), vomiting (6% to 17%), nausea (4% to 15%)

Hematologic: Hemoglobin decreased (18% to 21%), hematocrit decreased (13% to 18%), WBC decreased (12%), anemia (2% to 11%)

Hepatic: Serum alkaline phosphatase increased (9% to 22%), transaminases increased (2% to 18%), bilirubin increased (5% to 13%)

Local: Phlebitis/thrombophlebitis (18%)

Renal: Serum creatinine increased (3% to 11%)

Respiratory: Respiratory failure (2% to 20%), cough (6% to 11%), pneumonia (4% to 11%)

Miscellaneous: Infusion reaction (20% to 35%), septic shock (11% to 14%)

5% to 10%:

Cardiovascular: Hypertension (5% to 6%, children 9% to 10%)

Dermatologic: Erythema (4% to 9%), pruritus (6% to 7%)

Endocrine & metabolic: Hypomagnesemia (7%), hyperglycemia (6%)

Gastrointestinal: Mucosal inflammation (4% to 10%), abdominal pain (4% to 9%)

Genitourinary: Urinary tract infection (≤10%)

Hepatic: Albumin decreased (7%)

Local: Infection (1% to 9%, central line)

Renal: Hematuria (10%), blood urea nitrogen increased (4% to 9%)

Respiratory: Dyspnea (9%), pleural effusion (9%), respiratory distress (≤8%), rales (7%)

Miscellaneous: Sepsis (5% to 7%)

<5% (Limited to important or life-threatening):

Abdominal distention, anaphylaxis, anorexia, anxiety, appetite decrease, arrhythmia, arthralgia, atrial fibrillation, back pain, bacteremia, bradycardia, cardiac arrest, coagulopathy, confusion, constipation, depression, dizziness, dyspepsia, dystonia, edema, epistaxis, erythema multiforme, fatigue, febrile neutropenia, fluid overload, flushing, hematuria, hepatic necrosis, hepatomegaly, hepatotoxicity, hypercalcemia, hyperkalemia, hypoxia, infusion site reaction (pain/pruritus/swelling), insomnia, jaundice, liver, MI, nephrotoxicity (serum creatinine ≥2 × baseline value or ≥1 mg/dl in patients with serum creatinine above ULN range), pain (extremities), pancreatitis, petechiae, pulmonary edema, renal failure / insufficiency, seizure, skin exfoliation, skin lesion, somnolence, stridor, Stevens-Johnson syndrome, tachypnea, thrombocytopenia, tremor, urinary tract infection, urticarial, weakness; histamine-mediated reactions (including facial swelling, bronchospasm, sensation of warmth) have been reported.

10. DRUG INTERACTIONS

Cyclosporine (Systemic): May enhance the adverse/toxic effect of CASPOFUNGIN acetate. Cyclosporine (Systemic) may increase the serum concentration of CASPOFUNGIN acetate. Weight potential benefits of CASPOFUNGIN acetate against a possible elevated risk of hepatotoxicity. Monitor liver function and re-evaluate treatment in patients with abnormal values. Mild transaminase elevation may occur relatively commonly.

Tacrolimus: For patients receiving CASPOFUNGIN acetate and Tacrolimus, standard monitoring of Tacrolimus trough whole blood concentrations and appropriate Tacrolimus dosage adjustments are recommended.

Rifampin: Rifampin is a potent CY3A4 inducer and concomitant administration with CASPOFUNGIN acetate is expected to reduce the plasma concentrations of CASPOFUNGIN acetate. Therefore, adult patients on rifampin should receive 70 mg of CASPOFUNGIN acetate daily and pediatric patients on rifampin should receive 70 mg/m^2 of CASPOFUNGIN acetate daily (not to exceed an actual daily dose of 70 mg).

Other Inducers Hepatic CYP Enzymes Adults: When CASPOFUNGIN acetate is co-administered to adult patients with other inducers of hepatic CYP enzymes, such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, administration of a daily dose of 70 mg of CASPOFUNGIN acetate should be considered.

Pediatric Patients: When CASPOFUNGIN acetate is co-administered to pediatric patients with other inducers of hepatic CYP enzymes, such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, administration of a daily dose of 70 mg/m^2 CASPOFUNGIN acetate (not to exceed an actual daily dose of 70 mg) should be considered.

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii.

11. USE IN SPECIFIC POPUIATIONS

11.1 Pregnancy

Pregnancy Risk Factor: **C**

There are no adequate and well-controlled studies with the use of CASPOFUNGIN acetate in pregnant women.
CASPOFUNGIN acetate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
In offspring born to pregnant rats treated with CASPOFUNGIN acetate 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 acetate at doses comparable to 2 times the human dose based on body surface area comparisons, there was an increased incidence of incomplete ossification of the talus/calcaneus in offspring and increases in fetal resorptions.

11.2 Nursing Mothers

Excretion in breast milk unknown/use caution. It is not known whether CASPOFUNGIN acetate is present in human milk. Because many drugs are exercised when CASPOFUNGIN acetate is administered to a nursing woman.

11.3. Pediatric Use

The safety and effectiveness of CASPOFUNGIN acetate in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from prospective studies in pediatric patients 3 months to 17 years of age 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, Itraconazole).

The efficacy and safety of CASPOFUNGIN acetate has not been adequately studied in prospective clinical trials involving neonates and infants under 3 month of age.

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

Data not available regarding use in pediatric patients with hepatic impairment.

Adverse effects reported in ≥7% of pediatric patients receiving CASPOFUNGIN acetate include pyrexia, rash, decreased potassium, increased AST, diarrhea, increased ALT, chills, hypotension, vomiting, tachycardia, mucosal inflammation, hypertension, headache, erythema, central line infection, cough, respiratory distress, hypokalemia, abdominal pain, and pruritus.

11.4. Geriatric Use

Clinical studies of CASPOFUNGIN acetate did not include sufficient numbers of patients aged 65 and over to determine whether or efficacy were observed between these and younger patients. No dose adjustment is recommended for the elderly; however, greater sensitivity of some older individuals cannot be ruled out.

11.5. Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. CASPOFUNGIN acetate is not dialyzable; thus, supplementary dosing is not required following hemodialysis.

11.6 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 acetate 35 mg once daily is recommended based upon pharmacokinetic data. However recommended, a 70-mg loading dose should still be administered on Day 1. There is no clinical experience in adult patients with server hepatic impairment (Child –Pugh score greater than 9) and in pediatric patients 3 months to 17 years of age with any degree of hepatic impairment.

12. 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 acetate is not dialyzable. In clinical trials, one pediatric patient (16 years of age) unintentionally received a single dose of CASPOFUNGIN acetate of 113 mg (on Day 1), followed by 80 mg daily for an additional 7 days. No clinically significant adverse reactions were reported.

13. CLINICAL PHARMACOLOGY

13.1. Mechanism of Action

CASPOFUNGIN acetate inhibits synthesis of ß (1,3)-D-glucan, an essential component of the cell wall of susceptible fungi. Highest activity is in regions of active cell growth. Mammalian cells do not require ß (1,3)-D-glucan, limiting potential toxicity.

13.2. Pharmacokinetics

Distribution

Plasma concentrations of CASPOFUNGIN decline in a polyphasic manner following single 1 hour intravenous infusions.
A short α-phase occurs immediately post infusion, followed by a β-phase (half-life of 9 to 11 hours) that characterizes much of the profile and exhibits clear log.-linear behavior from 6 to 48 hours post-dose during which the plasma.
concentration decreases 10-fold. An additional, longer half-life phase, γ-p hase, (half-life of 40 to 50 hours), also occurs. 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. Mass balance results showed that approximately 92% of the administered radioactivity was distributed to tissues by 36 to 48 hours after a single 70 mg dose of [3H] CASPOFUNGIN. There is little excretion or biotransformation of CASPOFUNGIN 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, L-747969.
At later time points (5 or more days postdose), there is a low level (7 or less picomoles/mg protein, or 1.3% or less of the administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [3H] CASPOFUNGIN acetate, which may be due to two reactive intermediates formed during the chemical degradation of CASPOFUNGIN to L-747969. Additional metabolism involves hydrolysis into constitutive amino acids and their degradants, including dihydroxyhomotyrosine and N-acetyldihydroxy homotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Excretion

Two single-dose radiolabeled pharmacokinetic studies were conducted. In one study, plasma, urine, and feces were collected over 27 days, and in the second study plasma was collected over 6 months. Plasma concentrations of radioactivity and of CASPOFUNGIN were similar during the first 24 to 48 hours postdose; thereafter drug levels fell more rapidly.
In plasma, CASPOFUNGIN concentrations 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.
After single intravenous administration of [3H] CASPOFUNGIN, excretion of CASPOFUNGIN and its metabolites in humans was 35% of dose in feces and 41% of dose in urine. A small amount of CASPOFUNGIN is excreted unchanged in urine (approximately 1.4% of dose). Renal clearance of parent drug is low (approximately 0.15 mL/min) and total clearance of CASPOFUNGIN is 12 mL/min.

14. HOW SUPPLIED/STORAGE AND HANDLING

14.1. How supplied

Arofungin® (CASPOFUNGIN acetate) for injection is supplied in individual cartons as follows:

Arofungin ® 50 mg is a white to off-white lyophilized powder for reconstitution in a single dose glass vial with an aluminum cap and a red flip-off cap.

Arofungin ® 70 mg is a white to off- white lyophilized powder for reconstitution in a single dose glass vial with an aluminum cap and a orange flip-off cap.

14.2. Storage and Handling:

Arofungin ® (50 mg/vial or 70 mg/vial lyophilized powder) should be stored at 2° to 8°C (36° to 46° F). Retain in original package until time of use to protect from light. Reconstituted Arofungin® should be administered immediately after preparation because of microbiological concerns. Reconstituted solution should further be diluted in NS, 1/2NS, LR. Do not mix with dextrose-containing solutions.