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1 Caspofungin powder for concentrate for infusion

Caspofungin 50mg, powder for concentrate for infusion

Caspofungin 70mg, powder for concentrate for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Caspofungin 50 mg powder for concentrate for solution for infusion

Each vial contains 55.5 mg caspofungin acetate (equivalent to 50.0 mg caspofungin).

After reconstitution in 10.5 ml of water for injection, 1 ml of concentrate contains 5.2mg of caspofungin.

Caspofungin 70 mg powder for concentrate for solution for infusion

Each vial contains 77.7 mg caspofungin acetate (equivalent to 70.0 mg caspofungin).

After reconstitution in 10.5 ml of water for injection, 1 ml of concentrate contains 7.2mg of caspofungin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for infusion.

Before reconstitution, the powder is a white to off-white compact, powder.

The solution following reconstitution, is clear.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Caspofungin is indicated for:

- Empirical therapy for presumed fungal infections in febrile, neutropaenic patients
- Treatment of Invasive Candidiasis, including candidaemia, in neutropaenic and non-neutropaenic patients
- Treatment of Oesophageal Candidiasis
- Treatment of Oropharyngeal Candidiasis
- Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

4.2 Dose and method of administration

General Recommendations in Adult Patients

Caspofungin 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 neutropaenia. 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

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neutropaenia 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, 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 neutropaenic may warrant a longer course of therapy pending resolution of the neutropaenia.

The usual dose is 50 mg once daily (following a 70-mg loading dose for most indications). The safety and efficacy of a dose of 150 mg daily (range: 1 to 51 days; median: 14 days) have been studied in 100 adult patients with invasive candidiasis. The efficacy of caspofungin at this higher dose was not significantly better than the efficacy of the 50-mg daily dose of caspofungin. The efficacy of doses higher than 50 mg daily in the other adult patients for whom caspofungin is indicated is not known.

Oesophageal and Oropharyngeal 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 once daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

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 of 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 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 (3 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in paediatric patients (3 months to 17 years of age) should be based on the patient's body surface area (see section 6.6). 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 50 mg/m² daily thereafter (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualised to the indication, as described for each indication in adults (see above 'General Recommendations in Adult Patients').

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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 an actual daily dose of 70 mg). Although an increase in efficacy with 70 mg/m² daily has not been demonstrated, limited safety data suggest that an increase in dose to 70 mg/m² daily is well tolerated.

When caspofungin is co-administered to paediatric patients with inducers of medicine clearance, such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, use of 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. For instructions on reconstitution and dilution of the medicinal product see section 6.6.

4.3 Contraindications

Caspofungin is contraindicated in patients with hypersensitivity to any component of this product.

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

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 reactions.

Concomitant use of caspofungin with cyclosporine has been evaluated in healthy adult volunteers and in adult patients. Some healthy adult subjects who received two 3 mg/kg doses of cyclosporine 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 medicines. There was also an increase of approximately 35% in the area under the curve (AUC) of caspofungin when caspofungin and cyclosporine were co-administered; blood levels of cyclosporine remained unchanged. In a retrospective study of 40 patients treated during marketed use with caspofungin and cyclosporine for 1 to 290 days (median 17.5 days), no serious hepatic adverse events were noted. As expected in patients with allogeneic haematopoietic stem cell transplants or solid organ transplants, hepatic enzyme abnormalities occurred commonly; however, no patient had elevations in ALT that were considered medicine related. Elevations in AST considered at least possibly related to therapy with caspofungin and/or cyclosporine occurred in 5 patients, but all were less than 3.6 times the ULN. Discontinuations due to laboratory abnormalities in hepatic enzymes from any cause occurred in 4 patients. Of these, 2 were considered possibly related to therapy with caspofungin and/or cyclosporine as well as other possible causes. In the prospective invasive aspergillosis and compassionate use studies, there were 6 adult patients treated with caspofungin and cyclosporine for 2 to 56 days; none of these patients experienced increases in hepatic enzymes. These data suggest

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that caspofungin can be used in patients receiving cyclosporine when the potential benefit outweighs the potential risk.

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and in 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, isolated 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 evaluated for risk/benefit of continuing caspofungin therapy.

Paediatric Use

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 (see Indications):

- Empirical therapy for presumed fungal infections in febrile, neutropaenic patients
- Treatment of invasive candidiasis, including candidaemia, in neutropaenic and nonneutropaenic patients
- Treatment of oesophageal candidiasis
- Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

The efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

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

Use in the Elderly

The plasma concentration of caspofungin in healthy older men and women (65 years of age or more) was increased 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 seen in older patients relative to younger patients. No dosage adjustment is necessary for elderly patients (65 years of age or more).

4.5 Interaction with other medicines and other forms of interaction

Studies *in vitro* show that caspofungin acetate 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 medicines. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

In two adult clinical studies, cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) 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 cyclosporine. There were

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transient increases in liver ALT and AST when caspofungin and cyclosporine were co-administered. In a retrospective study of 40 patients treated during marketed use with caspofungin and/or cyclosporine for 1 to 290 days (median 17.5 days), no serious hepatic adverse events were noted (see section 4.4).

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

Caspofungin reduced the 12-hour blood concentration ($C_{12\text{hr}}$) of tacrolimus (FK-506) by 26% in healthy adult volunteers. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are recommended.

Results from two clinical medicine interaction studies in healthy adult volunteers indicate that rifampin both induces and inhibits caspofungin disposition with net induction at steady state. In one study, rifampin and caspofungin were co-administered for 14 days with both therapies initiated on the same day. In the second study, rifampin was administered alone for 14 days to allow the induction effect to reach steady state, and then rifampin and caspofungin were co-administered for an additional 14 days. When the induction effect of rifampin was at steady state, there was little change in caspofungin AUC or end-of-infusion concentration, but caspofungin trough concentrations were reduced by approximately 30%. The inhibitory effect of rifampin was demonstrated when rifampin and caspofungin treatments were initiated on the same day, and a transient elevation in caspofungin plasma concentrations occurred on Day 1 (approximately 60% increase in AUC). This inhibitory effect was not seen when caspofungin was added to pre-existing rifampin therapy, and no elevation in caspofungin concentrations occurred. In addition, results from population pharmacokinetic screening in adults suggest that co-administration of other inducers of medicine clearance (efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine) with caspofungin may also result in clinically meaningful reductions in caspofungin concentrations. Available data suggest that the inducible medicine clearance mechanism involved in caspofungin disposition is likely an uptake transport process, rather than metabolism. Therefore, when caspofungin is co-administered to adult patients with inducers of medicine clearance, such as efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of caspofungin should be considered (see section 4.2).

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 with inducers of medicine clearance, such as rifampin, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience involving pregnant women. In rats, caspofungin caused decreases in foetal body weights and an increase in the incidence of incomplete ossification of the skull and torso,

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at a maternally toxic dose of 5 mg/kg/day. In addition, at this same maternally toxic dose, there was an increase in the incidence of cervical rib in rats. Caspofungin has been shown to cross the placental barrier in animal studies.

Caspofungin should not be used during pregnancy unless clearly necessary.

Nursing Mothers

It is not known whether this medicine is excreted in human milk; therefore, women receiving caspofungin should not breast feed.

4.7 Effects on ability to drive and use machines

No data are available on whether caspofungin impairs the ability to drive or operate machinery.

4.8 Undesirable effects

Hypersensitivity reactions have been reported (see section 4.4).

Adult Patients

In clinical studies, 1865 adult individuals received single or multiple doses of caspofungin: 564 febrile neutropaenic patients (empirical therapy study), 382 patients with invasive candidiasis, 297 patients with oesophageal and/or oropharyngeal candidiasis, 228 patients with invasive aspergillosis and 394 individuals in phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone haematopoietic stem-cell transplantation. In the studies involving patients with documented *Candida* infections, the majority of the patients had serious underlying medical conditions (e.g. haematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the non-comparative *Aspergillus* study often had serious predisposing medical conditions (e.g. bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications. Reported medicine related clinical and laboratory abnormalities among all adults treated with caspofungin (total 1780) were typically mild and rarely led to discontinuation.

Common (> 1/100)

General: fever, headache, chills

GI: nausea, diarrhoea, vomiting

Liver: elevated liver enzyme levels (AST, ALT, alkaline phosphatase, direct and total bilirubin)

Blood: anaemia (decreased haemoglobin and haematocrit)

Peripheral Vascular: phlebitis/thrombophlebitis, infusion-site pruritus

Bone: arthralgia

Respiration: dyspnoea

Skin: rash, pruritus, sweating, erythema

Paediatric Patients

In clinical studies, 171 paediatric patients received single or multiple doses of caspofungin: 104 febrile, neutropaenic patients; 56 patients with invasive candidiasis; 1 patient with oesophageal candidiasis; and 10 patients with invasive aspergillosis. The overall clinical safety profile of caspofungin in paediatric patients is comparable to that in adult patients.

Reported medicine-related clinical and laboratory abnormalities among all paediatric patients treated with caspofungin (total 171) were typically mild and rarely led to discontinuation.

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Common (> 1/100)

General: fever, headache, chills

Liver: elevated liver enzyme levels (AST, ALT)

Cardiac: tachycardia

Peripheral Vascular: catheter site pain, flushing, hypotension

Skin: rash, pruritus

Post-Marketing Experience:

The following post-marketing adverse events have been reported:

Hepatobiliary: rare cases of hepatic dysfunction

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis and Stevens-Johnson syndrome

Cardiovascular: swelling and peripheral oedema

Laboratory abnormalities: hypercalcaemia; gamma-glutamyltransferase increased

Laboratory Test Findings

Adult Patients

Other medicine related laboratory abnormalities reported in adult patients were low albumin, low potassium, and decreased white blood cells.

Paediatric Patients

Other medicine-related laboratory abnormalities reported in paediatric patients were decreased potassium, hypomagnesaemia, increased glucose, decreased phosphorus, increased phosphorus, and increased eosinophils.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

In clinical studies, the highest dose was 210 mg, which was administered as a single dose to 6 healthy adult subjects and was generally well tolerated. In addition, a dose of 150 mg daily up to 51 days has been administered to 100 healthy patients and was generally well tolerated. Caspofungin is not dialysable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimycotics for systemic use, ATC Code: J02AX04

Caspofungin is a sterile, lyophilised product for intravenous infusion that contains a semisynthetic lipopeptide (echinocandin) compound synthesised from a fermentation product of *Glarea lozoyensis*. Caspofungin is the first of a new class of antifungal medicines (echinocandins) that inhibit the synthesis of β (1,3)-D-glucan, an integral component of the fungal cell wall.

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Actions

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 lusitanae*, *Candida parapsilosis*, *Candida rugosa*, and *Candida tropicalis*). 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-A (for *Aspergillus* species) and method M27-A (for *Candida* species).

Interpretive standards (or breakpoints) for caspofungin against *Candida* species are applicable only to tests performed using CLSI microbroth dilution reference method M27-A3 for minimum inhibitory concentrations (MIC) read as a partial inhibition endpoint at 24 hours. The MIC values for caspofungin using CLSI microbroth dilution reference method M27-A3 should be interpreted according to the criteria provided in Table 1 below (CLSI M27-S3).

Table 1
Susceptibility Interpretive Criteria for Caspofungin against *Candida* species

Pathogen	Broth Microdilution MIC*, † (µg/mL) at 24 hours			
	Susceptible	Indeterminate	Resistant	Non-susceptible
<i>Candida</i> species	≤2	-	-	≥2

* A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.
† There is no Resistant category assigned for the echinocandin agents; isolates with higher MICs may be described as Non-susceptible.

There are no established breakpoints for caspofungin against *Candida* species using the European Committee for Antimicrobial Susceptibility Testing (EUCAST) method.

Standardised techniques for susceptibility testing have been established for yeasts by EUCAST. No standardised techniques for susceptibility testing or interpretive breakpoints have been established for *Aspergillus* species and other filamentous fungi using either the CLSI or EUCAST method.

Activity *in vivo*

Caspofungin was 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 was also active in immunodeficient animals after disseminated infection with *C. glabrata*, *C. krusei*, *C. lusitanae*, *C. parapsilosis*, or *C. tropicalis* in which the endpoint was clearance of *Candida* from target organs. In a lethal, rat pulmonary-infection model with *A. fumigatus*, caspofungin was 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.

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Medicine Resistance

A caspofungin MIC of ≤ 2 $\mu\text{g/mL}$ ("Susceptible" per Table 1) using the CLSI M27-A3 method indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations > 2 $\mu\text{g/mL}$ for growth inhibition have developed in a mouse model of *C. albicans* infection. Isolates of *Candida* with reduced susceptibility to caspofungin have been identified in a small number of patients during treatment (MICs for caspofungin > 2 $\mu\text{g/mL}$ using standardised 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 associated with poor clinical outcomes.

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

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

Medicine Interactions

In vitro and *in vivo* studies of caspofungin acetate, in combination with amphotericin B, demonstrate no antagonism of antifungal activity against either *A. fumigatus* or *C. albicans*. Results from *in vitro* studies suggest that there was some evidence of additive/indifferent or synergistic activity against *A. fumigatus* and additive/indifferent activity against *C. albicans*. The clinical significance of these results is unknown.

5.2 Pharmacokinetic properties

Absorption

Absorption is not relevant since caspofungin acetate is administered intravenously.

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 with a half-life of 9 to 11 hours that characterises much of the profile and exhibits clear log-linear behaviour from 6 to 48 hours post-dose, during which the plasma concentration decreases by 10-fold. An additional γ -phase also occurs (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. 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 acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

Metabolism

Caspofungin is slowly metabolised by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound. At later time points (≥ 5 days post-dose), there is a low level (≤ 7 picomoles/mg protein, or $\leq 1.3\%$ of administered dose) of covalent binding of radiolabel in plasma following single-dose administration of [^3H] caspofungin acetate, which

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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

Two single-dose, radiolabelled pharmacokinetic studies were conducted. In one study, plasma, urine, and faeces were collected over 27 days, and in the second study plasma was collected over 6 months. Approximately 75% of the radioactivity was recovered: 41% in urine and 34% in faeces. Plasma concentrations of radioactivity and of caspofungin were similar during the first 24 to 48 hours post-dose; thereafter medicine levels fell more rapidly. In plasma, caspofungin concentrations fell below the limit of quantitation after 6 to 8 days post-dose, while radiolabel fell below the limit of quantitation at 22.3 weeks postdose. A small amount of caspofungin is excreted unchanged in urine (approximately 1.4% of dose). Renal clearance of parent medicine is low (approximately 0.15 mL/min).

Characteristics in Patients

Gender

The plasma concentration of caspofungin was similar in healthy men and women on Day 1 following a single 70 mg dose. After 13 daily 50 mg doses, the caspofungin plasma concentration in some women was elevated approximately 20% relative to men.

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) were increased by approximately 55% in AUC compared to healthy control subjects. In a 14 day multiple-dose study (70 mg on Day 1 followed by 50 mg daily thereafter), plasma concentrations in adult patients with mild hepatic insufficiency were increased modestly (19 to 25% in AUC) on Days 7 and 14 relative to healthy control subjects.

Paediatric Patients

Caspofungin has been studied in five prospective studies involving paediatric patients under 18 years of age, including three paediatric pharmacokinetic studies (initial study in adolescents [12-17 years of age] and children [2-11 years of age] followed by a study in younger patients [3-23 months of age] and then followed by a study in neonates and infants [<3 months]).

- In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m² daily (maximum 70 mg daily), the caspofungin plasma AUC_{0-24hr} was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses >50 mg daily, and, in fact, 6 of 8 received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.
- In children (ages 2 to 11 years) receiving caspofungin at 50 mg/m² daily (maximum 70 mg daily), the caspofungin plasma AUC_{0-24hr} after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day. On the first day of administration, AUC_{0-24hr} was somewhat higher in children than adults for these comparisons (37% increase for the 50 mg/m²/day to 50 mg/day comparison). However, it should be recognised that the AUC values in these children on Day 1 were still less than those seen in adults at steady-state conditions.

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- In young children and toddlers (ages 3 to 23 months) receiving caspofungin at 50 mg/m² daily (maximum 70 mg daily), the caspofungin plasma AUC_{0-24hr} after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg daily. As in the older children, these young children who received 50 mg/m² daily had slightly higher AUC_{0-24 hr} values on Day 1 relative to adults receiving the standard 50-mg daily dose. The caspofungin pharmacokinetic results from the young children (3 to 23 months of age) that received 50 mg/m² caspofungin daily were similar to the pharmacokinetic results from older children (2 to 11 years of age) that received the same dosing regimen.
- In neonates and infants (<3 months) receiving caspofungin at 25 mg/m² daily, caspofungin peak concentration (C_{1 hr}) and caspofungin trough concentration (C_{24 hr}) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, C_{1 hr} was comparable and C_{24 hr} modestly elevated (36%) in these neonates and infants relative to adults. AUC_{0-24hr} measurements were not performed in this study due to the sparse plasma sampling. Of note, the efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

5.3 Preclinical safety data

Acute Toxicity

The approximate intravenous lethal dose₅₀ (LD₅₀) for female mice and rats was calculated as 19 and 38 mg/kg, respectively.

Chronic Toxicity

Several treatment-related changes were noted in intravenous toxicity studies in rats and Rhesus monkeys. In these studies, signs of histamine release were observed in rats, serum transaminase levels were increased in monkeys, and injection-site irritation was seen in both species.

In 5 and 14 week intravenous toxicity studies in rats, 5 mg/kg/day produced signs of histamine release consisting of hyperaemia and swelling of the extremities, sluggish movement or ataxia, and recumbency. These signs occurred only during the first 7 to 9 days of dosing presumably due to endogenous histamine depletion. Overall, in the rat studies, 2 mg/kg/day was established as the no-effect level for histamine release. No signs of histamine release were reported in 5, 14, and 27 week intravenous dosing studies in monkeys. In ancillary pharmacology studies, a 20 minute infusion at 8 mg/kg produced no adverse effects in monkeys; however, bolus injections of 5 or 8 mg/kg did produce signs of histamine release. Similar signs of histamine release that were produced with a structural analog of caspofungin acetate in monkeys were reversed upon injection of cyproheptadine.

In 5, 14, and 27 week intravenous toxicity studies in monkeys, ALT and/or AST levels increased slightly, but these levels returned to baseline or remained slightly elevated over the course of the studies. In one 5 week study, scattered small foci of subcapsular necrosis were observed microscopically in the livers of some animals; however, this histopathological finding was not seen in other studies of up to 27 weeks duration at the same or higher doses. The no-effect level for serum transaminase elevations after intravenous treatment was 1.5 mg/kg/day in monkeys, and greater than 7.2 mg/kg/day in rats (the highest dose tested).

During the 5, 14, and 27 week intravenous toxicity studies in rats and monkeys, clinical and histopathological signs of injection-site irritation were observed. Overall, the no-effect dosage level

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for irritation at the injection site in rats was 1.8 mg/kg/day (0.18 mg/mL), and in monkeys it was 3 mg/kg/day (0.25 mg/mL). Effective pre- and post-dose flushing of catheter lines minimised injection-site irritation in animal studies.

Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of caspofungin.

Mutagenesis

Caspofungin acetate was evaluated in the following series of *in vitro* assays and found to be neither mutagenic nor genotoxic: bacterial (Ames) and mammalian cell (V79 Chinese hamster lung fibroblasts) mutagenesis assays, the alkaline elution/rat hepatocyte DNA strand break test, and the chromosomal aberration assay in Chinese hamster ovary cells. Additionally, in the *in vivo* mouse bone marrow chromosomal test, caspofungin acetate was not genotoxic at doses up to 12.5 mg/kg, administered intravenously.

Reproduction

Female rats administered 0.5, 2, and 5 mg/kg/day of caspofungin acetate intravenously for 16 days prior to cohabitation, during cohabitation, and through gestation Day 7 showed no medicine-related effects on mating performance, fecundity, fertility, or embryonic survival.

Male rats treated intravenously with 0.5, 2, and 5 mg/kg/day (maximum dosage tested) for 28 days prior to mating showed no effect on fertility.

Development

In rats, there were no developmental effects at a dose of 2 mg/kg/day. At a maternally toxic dose of 5 mg/kg/day, which resulted in a plasma exposure approximately 1.5 times the plasma exposure seen in humans administered 70 mg, caspofungin caused decreases in foetal body weights and an increase in the incidence of incomplete ossification of the skull and torso. In addition, at this same maternally toxic dose, there was an increase in the incidence of cervical rib in rats.

In rabbits, there were no treatment-related external, visceral, or skeletal foetal morphological findings in an intravenous toxicity study where caspofungin acetate was administered to pregnant rabbits at dosages of 1, 3, and 6 mg/kg/day on gestation days 7 through 20. Therefore, the no-effect level for developmental toxicity was greater than 6 mg/kg/day. The no-effect level for maternal toxicity (based on minimal decreases in average maternal body weight gain and food consumption) was 3 mg/kg/day. Pregnant rabbits administered 5 mg/kg/day had plasma exposures approximately 1.5 times the plasma exposure seen in humans administered 70 mg.

Caspofungin acetate has been shown to cross the placental barrier in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Mannitol

Hydrochloric acid, concentrate (to adjust the pH)

Sodium hydroxide (to adjust the pH)

Carbon dioxide (to adjust the pH)

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6.2 Incompatibilities

Do not mix with diluents containing glucose, as caspofungin is not stable in diluents containing glucose. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

~~18-24~~ months.

Reconstituted concentrate (following reconstitution, prior to dilution for infusion):

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C or less when reconstituted with either 0.9% Sodium Chloride injection or lactated Ringer's solution.

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.

Diluted patient infusion solution:

Chemical and physical in-use stability of the diluted patient infusion solution has been demonstrated for 48 hours at 2 to 8°C and for 24 hours at 25 °C or less, when 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 powder for concentrate for infusion contains no preservative. 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.

6.4 Special precautions for storage

Unopened vials: Store in a refrigerator 2°C - 8°C.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Caspofungin 50 mg powder for concentrate for solution for infusion

10 ml Type I glass vial with a bromobutyl rubber stopper and an aluminium flip-off seal with a top red plastic flip-off cap. Supplied in packs of 1 vial.

Caspofungin 70 mg powder for concentrate for solution for infusion

10 ml Type I glass vial with a bromobutyl rubber stopper and an aluminium flip-off seal with a top orange plastic flip-off cap. Supplied in packs of 1 vial.

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6.6 Special precautions for disposal and other handling

Reconstitution of Caspofungin powder for concentrate for infusion

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 MEDICATIONS, as there is no data available on the compatibility of caspofungin with other intravenous substances, additives, or medications. Visually inspect the infusion solution for particulate matter or discolouration.

Refer to section 6.3 for information on chemical-physical in-use shelf life after reconstitution and dilution.

Instructions for use in Adults

Step 1 - Reconstitution of vials

To reconstitute the powdered medicine, bring the refrigerated vial of caspofungin powder for concentrate for infusion to room temperature and aseptically add 10.5 mL of 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 discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25°C.

Step 2 - Addition of Reconstituted Caspofungin powder for concentrate for infusion, 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 medicine (as shown in the table below) to a 250 mL intravenous 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 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. Caspofungin should be administered by slow intravenous infusion over approximately 1 hour.

PREPARATION OF THE PATIENT INFUSION SOLUTIONS IN ADULTS

DOSE*	Volume of reconstituted Caspofungin for transfer to intravenous bag or bottle	Typical preparation (reconstituted Caspofungin added to 250 mL) final concentration	Reduced volume infusion (reconstituted Caspofungin 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	0.47 mg/mL
35 mg for moderate hepatic insufficiency (from one 70 mg vial)	5 mL	0.14 mg/mL	0.34 mg/mL

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35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 mL	0.14 mg/mL	0.34 mg/mL
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* 10.5 mL should be used for reconstitution of all vials

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

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):

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

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 Caspofungin powder for concentrate for infusion 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 7.2 mg/mL.
4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)^c 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)^c 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.
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 (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/m² infusion for paediatric patients >3 months of age (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:

$$BSA (m^2) \times 50 \text{ mg} / m^2 = \text{Daily Maintenance Dose}$$

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

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2. Equilibrate the refrigerated vial of Caspofungin powder for concentrate for infusion 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.
4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)^c 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)^c 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 0.5mg/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/m² infusion for paediatric patients 3 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) Caspofungin is formulated to provide the full labelled vial dose (70 mg or 50 mg) when 10 mL is withdrawn from the vial.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd, P O Box 65 231, Mairangi Bay, Auckland 0754

Ph:(09) 815 2664.

9 DATE OF FIRST APPROVAL

04 October 2018

10 DATE OF REVISION OF THE TEXT

~~04 October 2018~~ 16 October 2018

SUMMARY TABLE OF CHANGES

N/A

NEW ZEALAND DATA SHEET

<u>Date of Revision</u>	<u>Section Changed</u>	<u>Summary of new information</u>
<u>16 October 2018</u>	<u>6.3</u>	<u>Shelf life extended from 18 to 24 months</u>