PROFESSIONAL INFORMATION

IVECAS IV RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

IVECAS 50 IV powder for solution for infusion

IVECAS 70 IV powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IVECAS 50 IV:

Each 10 mL vial contains caspofungin acetate equivalent to caspofungin 50 mg.

The reconstituted solution contains caspofungin 5,2 mg per 1 mL solution.

Excipient with known effect:

Contains sugar (sucrose and the sugar alcohol, mannitol).

Each 50 mg vial contains sucrose 35,7 mg and mannitol 23,8 mg.

IVECAS 70 IV:

Each 10 mL vial contains caspofungin acetate equivalent to caspofungin 70 mg.

The reconstituted solution contains caspofungin 7,2 mg per 1 mL solution.

Excipient with known effect:

Contains sugar (sucrose and the sugar alcohol mannitol).

Each 70 mg vial contains sucrose 50,0 mg and mannitol 33,3 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

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

Reconstituted solution:

- pH: 5,5 - 7,5
- osmolality: NMT 100 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IVECAS is indicated in adults for:

- empirical therapy for presumed fungal infections in febrile, neutropenic patients
- treatment of invasive candidiasis, including candidaemia
- treatment of oesophageal candidiasis, where intravenous (IV) antifungal therapy is appropriate
- treatment of oropharyngeal candidiasis, where IV antifungal therapy is appropriate
- treatment of invasive aspergillosis in patients who are refractory to, or intolerant of other therapies, including amphotericin B, lipid formulations of amphotericin B and itraconazole.

Paediatric use

The safety and effectiveness of IVECAS 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.

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

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

4.2 Posology and method of administration

Posology

General recommendations in adult patients

Empirical therapy

A single 70 mg loading dose should be administered on day 1, followed by 50 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. If the 50 mg 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 neutropenic may warrant a longer course of therapy pending resolution of the neutropenia.

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 daily thereafter. Duration of treatment should be based upon the severity of the patient’s underlying disease, recovery from immunosuppression, and clinical response. The efficacy of doses above 70 mg is not known.

Safety data suggests that an increase in dose to 70 mg daily is well tolerated. The efficacy of doses above 70 mg has not been adequately studied in patients with invasive aspergillosis.

Special populations

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

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

When co-administering IVECAS in adult patients with the metabolic inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg of IVECAS, should be considered (see section 4.5).

Patients with hepatic insufficiency

Adult patients with mild hepatic insufficiency (Child-Pugh score 5 - 6):

No dose adjustment is required.

Adult patients with moderate hepatic impairment (Child-Pugh score 7 - 9):

35 mg IVECAS per day is recommended. However, where recommended, a 70 mg loading dose should still be administered on day 1.

Severe hepatic impairment:

There is no clinical experience in adult patients with severe hepatic insufficiency (Child-Pugh score > 9) (see section 4.3) and in paediatric patients with any degree of hepatic insufficiency.

Paediatric population

IVECAS should be administered in children and adolescents by slow IV infusion over approximately 1 hour.

Dosing in children and adolescents (3 months to 17 years of age) should be based on the patient's body surface area (see section 6.1 "Instructions for use in paediatric patients", Mosteller[1] formula).

For all indications a single 70 mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg

daily). Duration of treatment should be individualised to the indication, as described for each indication in adults (see “General recommendation in adult patients”, above).

[1] Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987 Oct 22;317(17): 1098 (letter)

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

When co-administering caspofungin, as in IVECAS, to paediatric patients with metabolic inducers such as efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine, use of a daily dose of 70 mg/m^2 of IVECAS (not to exceed an actual daily dose of 70 mg), should be considered (see section 4.5).

Method of administration

IVECAS SOLUTION should be administered in by slow intravenous infusion over approximately 1 hour. For instructions for reconstitution and further dilution, see section 6.6.

IVECAS should be given as a single infusion.

4.3 Contraindications

- hypersensitivity to caspofungin or to any of the ingredients of IVECAS, listed in section 6.1
- severe hepatic insufficiency, as caspofungin as in IVECAS has not been studied in these patients.

4.4 Special warnings and precautions for use

Limited data suggest that less common non-*Candida* yeasts and non-*Aspergillus* moulds are not covered by caspofungin (contained in IVECAS). The efficacy of caspofungin against these fungal

pathogens has not been established.

Hypersensitivity reactions

Anaphylaxis has been reported during administration of caspofungin, as in IVECAS. If this occurs, IVECAS should be discontinued and appropriate treatment administered.

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 (see section 4.8).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post marketing use of caspofungin (as in IVECAS). Caution should apply in patients with history of allergic skin reactions (see section 4.8).

Concomitant use with ciclosporin

Transient increases in alanine transaminase (ALT) and aspartate transaminase (AST) of less than or equal to 3-fold the upper limit of normal (ULN) may occur when caspofungin, as in IVECAS, is given concomitantly with ciclosporin. These increases can be resolved with discontinuation of these medicines (see section 4.5).

There is an increase of approximately 35 % in the area under the curve (AUC) of caspofungin when IVECAS and ciclosporin are co-administered; blood levels of ciclosporin remain unchanged. IVECAS should only be used in patients receiving ciclosporin when the potential benefit outweighs the potential risk. Close monitoring of liver enzymes should be considered if IVECAS and ciclosporin are used concomitantly.

Hepatic impairment

In adult patients with mild and moderate hepatic impairment, the AUC can be increased by about 20 % and 75 %, respectively (see sections 5.2 and 4.2).

A reduction of the daily dose to 35 mg is recommended for adults with moderate hepatic impairment

(see section 4.2).

There is no clinical experience in adults with severe hepatic impairment or in paediatric patients with any degree of hepatic impairment. A higher exposure than in moderate hepatic impairment is expected and IVECAS should not be used in these patients (see section 4.3).

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and paediatric patients treated with caspofungin (as in IVECAS). In some adult and paediatric patients with serious underlying conditions who were also receiving multiple concomitant medicines, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported; a causal relationship to caspofungin (as in IVECAS) has not been established.

Patients who develop abnormal liver function tests during treatment with IVECAS should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing therapy should be re-evaluated.

Information on excipients of IVECAS

IVECAS contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not receive IVECAS.

IVECAS contains less than 1 mmol (0,023 mg) sodium per 10 mL, that is to say essentially 'sodium free'

4.5 Interaction with other medicines and other forms of interaction

In vitro, caspofungin is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system and does 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. However, caspofungin did interact with other medicines in pharmacological and clinical studies (see below).

Limited data from population pharmacokinetics show that concomitant use of IVECAS with the inducers efavirenz, nevirapine, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose

of caspofungin to 70 mg following the 70 mg loading dose, should be considered in adult patients (see section 4.2).

In vitro and *in vivo* studies of caspofungin in combination with amphotericin B, does not result in 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.

Ciclosporin

Ciclosporin A increases the AUC of caspofungin (as in IVECAS) by approximately 35 %. The increase in AUC is probably due to reduced uptake of caspofungin by the liver. Caspofungin does not increase the plasma levels of ciclosporin.

There are transient increases in liver ALT and AST of less than or equal to 3-fold the ULN when IVECAS and ciclosporin are co-administered, which should resolve with discontinuation of both these medicines (see section 4.4).

Close monitoring of liver enzymes should be considered if the two medicines are used concomitantly.

Tacrolimus

Caspofungin, as in IVECAS, reduces the trough concentration of tacrolimus by 26 % in healthy subjects. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are essential.

Rifampicin

IVECAS does not influence the pharmacokinetics of rifampicin, however rifampicin may cause a 60 % increase in AUC and 170 % increase in trough concentration of caspofungin on the first day of co-administration when both medicines are initiated together. Caspofungin trough levels gradually decrease

upon repeated administration. After two weeks' administration rifampicin has limited effect on AUC, but trough levels are 30 % lower than in adult patients who receive IVECAS alone. The mechanism of interaction may possibly be due to an initial inhibition and subsequent induction of transport proteins. A similar effect could be expected for other medicines that induce metabolic enzymes.
Data suggest that the inducible medicine clearance mechanism involved in caspofungin disposition is likely an uptake transport process, rather than metabolism. Therefore, when IVECAS is co-administered to adult patients with inducers of medicine clearance, such as efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine, use of a daily dose of 70 mg of IVECAS should be considered (see section 4.2)

Clinical studies in adult healthy volunteers show that medicines such as itraconazole, amphotericin B, mycophenolate, nelfinavir or tacrolimus do not alter the pharmacokinetics of caspofungin. IVECAS has no effect on the pharmacokinetics of itraconazole, amphotericin B, rifampicin, or the active metabolite of mycophenolate.

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

Paediatric population

In paediatric patients, co-administration of dexamethasone with caspofungin, as in IVECAS, may result in clinically meaningful reductions in caspofungin trough concentrations. Paediatric patients may possibly have similar reductions with inducers as seen in adults.
When caspofungin as in IVECAS is co-administered to paediatric patients (12 months to 17 years of age) with inducers of medicine clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, an IVECAS dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

IVECAS should not be used during pregnancy as there is no clinical experience involving pregnant women.

Animal studies have shown developmental toxicity. Caspofungin has been shown to cross the placental barrier in animal studies.

Breastfeeding

It is not known whether caspofungin as in IVECAS is excreted in human milk; therefore, women receiving IVECAS should not breastfeed their babies.

Available pharmacodynamic/ toxicological data in animals have shown excretion of caspofungin in milk.

Fertility

There are no clinical data for caspofungin, as in IVECAS, to assess its impact on fertility.

4.7 Effects on ability to drive and use machines

IVECAS may cause dizziness, somnolence and blurred vision. Patients should be advised not to drive or operate machinery or tools until they know how treatment with IVECAS affects them.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity reactions (anaphylaxis and possibly histamine-mediated adverse reactions) have been reported (see section 4.4).

Also reported in patients with invasive aspergillosis were pulmonary oedema, adult respiratory distress syndrome (ARDS), and radiographic infiltrates.

a. Adult patients

Phlebitis was a commonly reported local injection-site adverse reaction in all patient populations. Other local reactions included erythema, pain/tenderness, itching, discharge, and a burning sensation. Reported clinical and laboratory abnormalities among all adults treated with caspofungin were typically mild and rarely led to discontinuation.

Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequent Less frequent	Decreased haemoglobin, decreased haematocrit, anaemia, decreased white blood cell count Thrombocytopaenia, coagulopathy, leucopaenia, eosinophil count increased, decreased platelet count, increased platelet count, decreased lymphocyte count, increased white blood cell count, decreased neutrophil count
Immune system disorders	Frequency unknown	Hypersensitivity reactions (anaphylaxis and possibly histamine-mediated adverse reactions) (see section 4.4)
Metabolism and nutrition disorders	Frequent Less frequent	Hypokalaemia Fluid overload, hypomagnesaemia, anorexia, electrolyte imbalance, hyperglycaemia, hypocalcaemia, metabolic acidosis

Psychiatric disorders	Less frequent	Anxiety, disorientation, insomnia
Nervous system disorders	Frequent Less frequent	Headache Dizziness, dysgeusia, paraesthesia, somnolence, tremor, hypaesthesia
Eye disorders	Less frequent	Ocular icterus, vision blurred, eyelid oedema, increased lacrimation
Cardiac disorders	Less frequent	palpitations, tachycardia, dysrhythmia, atrial fibrillation, congestive cardiac failure
Vascular disorders	Frequent Less frequent Frequency unknown	Phlebitis Thrombophlebitis, flushing, hot flush, hypertension, hypotension Swelling, peripheral oedema
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent Frequency unknown	Dyspnoea Nasal congestion, pharyngolaryngeal pain, tachypnoea, bronchospasm, cough, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing Pulmonary oedema, adult respiratory distress syndrome (ARDS) and radiographic infiltrates
Gastrointestinal disorders	Frequent Less frequent	Nausea, diarrhoea, vomiting Abdominal pain, abdominal pain upper, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia, flatulence

Hepatobiliary disorders	Frequent	Elevated liver values (alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood alkaline phosphatase, conjugated bilirubin, blood bilirubin)
	Less frequent	Cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, abnormal hepatic function, hepatotoxicity, liver disorder, increased gamma-glutamyl transferase (GGT)
	Frequency unknown	Hepatic dysfunction
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, erythema, hyperhidrosis
	Less frequent	Erythema multiforme, macular rash, maculopapular rash, pruritic rash, urticaria, allergic dermatitis, generalised pruritus, erythematous rash, generalised rash, morbilliform rash, skin lesion
	Frequency unknown	Toxic epidermal necrolysis and Stevens-Johnson syndrome (see section 4.4)
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia
	Less frequent	Back pain, pain in extremity, bone pain, muscular weakness, myalgia
Renal and urinary disorders	Less frequent	Renal failure, acute renal failure

General disorders and administrative site conditions	Frequent Less frequent	Pyrexia, chills, infusion site pruritus Pain, catheter site pain, fatigue, feeling cold, feeling hot, infusion site erythema, infusion site induration, infusion site pain, infusion site swelling, injection site phlebitis, oedema peripheral, tenderness, chest discomfort, chest pain, face oedema, feeling of body temperature change, induration, infusion site extravasation, infusion site irritation, infusion site phlebitis, infusion site rash, infusion site urticaria, injection site erythema, injection site oedema, injection site pain, injection site swelling, malaise, oedema

Investigations	Frequent	Decreased blood potassium, decreased blood albumin
	Less frequent	Increased blood creatinine, positive red blood cells urine, decreased total protein, protein urine present, prolonged prothrombin time, shortened prothrombin time, decreased blood sodium, increased blood sodium, increased blood calcium, decreased blood chloride, decreased blood phosphorus, increased blood phosphorus, increased blood urea, prolonged activated partial thromboplastin time, decreased blood bicarbonate, increased blood chloride, increased blood potassium, decreased blood uric acid, blood urine present, abnormal breath sounds, decreased carbon dioxide, increased immunosuppressant medicine level, international normalised ratio increased, urinary casts, positive white blood cells urine, and increased pH urine.

b. Paediatric patients

The most common medicine related clinical adverse experiences reported in paediatric patients treated with caspofungin (as in IVECAS) were pyrexia, rash and headache.

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequent	Eosinophil counts increased
Nervous system disorders	Frequent	Headache
Cardiac disorders	Frequent	Tachycardia
Vascular disorders	Frequent	Flushing, hypotension
Hepatobiliary disorders	Frequent	Elevated liver enzyme levels (AST, ALT)
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
General disorders and administration site conditions	Frequent	Fever, chills, catheter site pain
Investigations	Frequent	Decreased potassium, hypomagnesaemia, increased glucose, decreased phosphorus, and increased phosphorus

Reporting of suspected adverse reactions

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 to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

In clinical studies, the highest dose was 210 mg, which was administered as a single dose to 6 adult subjects and was generally well tolerated. In addition, a dose of 150 mg once daily up to 51 days has been administered to 100 adult patients and was generally well tolerated.

Management of overdose:

Caspofungin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antimycotics for systemic use.

ATC code: J02AX04

Pharmacological classification: A 20.2.2 Antimicrobial (chemotherapeutic agents): Fungicides

Mechanism of action

Caspofungin acetate inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of many filamentous fungi and yeasts. Beta (1,3)-D-glucan is not present in mammalian cells. Fungicidal activity with caspofungin has been demonstrated against *Candida* and *Aspergillus* species.

Resistance

Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment.

A caspofungin minimal inhibitory concentration (MIC) of < 2 micrograms/mL using the Clinical and Laboratory Standards Institute (CLSI) M27-A3 method indicates that the *Candida* isolate is likely to be inhibited, if caspofungin therapeutic concentrations are achieved; there is insufficient treatment outcome information on isolates with reduced caspofungin susceptibility to define categories other than

susceptible. Breakthrough infections with *Candida* isolates requiring caspofungin concentration > 2 micrograms/mL for growth inhibition have developed in a mouse model of *C. albicans* infection and in some patients with *Candida*- infections. Some of these isolates had mutations in the FKS1 gene. Development of *in vitro* resistance to caspofungin by *Aspergillus* species has been identified. In limited clinical experience, resistance to caspofungin in patients with invasive *aspergillosis* has been observed. The mechanism of resistance has not been established. The incidence of resistance to caspofungin in various clinical isolates of *Candida*- and *Aspergillus* species is unknown. Caspofungin resistance in *Candida* has been observed, but the incidence may differ by species or region.
Less frequently non-*Candida* yeasts and non-*Aspergillus* moulds are not sensitive to caspofungin. The efficacy of caspofungin against these fungal pathogens has not been established.

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.

5.2 Pharmacokinetic properties

Distribution:

Plasma concentrations of caspofungin decline in a polyphasic manner following single 1 hour intravenous infusions. A short alpha-phase occurs immediately post-infusion, followed by a beta-phase with a half-life of 9 - 11 hours that characterises much of the profile and exhibits clear log-linear behaviour from 6 - 48 hours post-dose during which the plasma concentration decreases by 10-fold. An additional gamma-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. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration.

Biotransformation:

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 of covalent binding, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin. Additional metabolism involves hydrolysis into constitutive amino acids and their derivatives, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Elimination:

Two single-dose radio-labelled 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 - 48 hours post-dose; thereafter medicine levels fell more rapidly. In plasma, caspofungin concentrations fall below the limit of quantitation 6 to 8 days post-dose, while radio-label fell below the limit of quantitation at 22,3 weeks post-dose. A small amount of caspofungin is excreted unchanged in urine (approximately 1,4 % of the administered dose).

Renal clearance of the parent substance is low (approximately 0,15 mL/min).

Pharmacokinetics in special patient groups

Paediatric population

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

In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2 daily, the caspofungin plasma $AUC_{0\text{-}24h}$ 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 - 11 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24h}$ after multiple doses was comparable to that seen in adults receiving caspofungin at 50 mg/day.
On the first day of administration, $AUC_{0\text{-}24hr}$ was somewhat higher in children than adults for these comparisons (37 % increase for
the 50 mg/m^2/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.

In young children and toddlers (ages 3 - 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24h}$ 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/m^2 daily had slightly higher $AUC_{0\text{-}24hr}$ values on day 1 relative to adults receiving the standard 50 mg daily dose. The caspofungin pharmacokinetic results from the young children (3 - 23 months of age) that received 50 mg/m^2 caspofungin daily were similar to the pharmacokinetic results from older children (2 - 11 years old) that received the same dosing regimen.

In neonates and infants (< 3 months) receiving caspofungin at 25 mg/m^2 daily, caspofungin peak concentration (C_{1hr}) and caspofungin trough concentration (C_{24hr}) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On day 1, C_{1hr}, was comparable and C_{24hr} modestly elevated (36 %) in these neonates and infants relative to adults. $AUC_{0\text{-}24hr}$ measurements were

not performed in this study due to the sparse plasma sampling.

The efficacy and safety of caspofungin have not been adequately studied in infants under 3 months of age and IVECAS is therefore not indicated for this age group.

Gender

The plasma concentration of caspofungin is 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 may be elevated approximately 20 % relative to men.

Elderly patients

The plasma concentration of caspofungin in healthy older men and women (aged > 65 years) is increased by approximately 28 % in area under the curve (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. However, no dosage adjustment is necessary for elderly patients.

Hepatic insufficiency

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

Plasma concentrations in patients with mild hepatic insufficiency are increased modestly (19 - 25 % in AUC) on days 7 and 14 relative to healthy subjects. A reduction of the daily dose to 35 mg in moderate hepatic impairment can provide an AUC similar to that obtained in subjects with normal hepatic function, receiving the standard regimen.

No data are available on patients with severe hepatic insufficiency (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid

Mannitol

Sodium hydroxide (for pH adjustment)

Sucrose

6.2 Incompatibilities

DO NOT use any diluents containing dextrose (alpha-D-glucose), as IVECAS is not stable in such diluents.

In the absence of compatibility studies, IVECAS must not be mixed with other medicines.

6.3 Shelf life

Storage of the product before reconstitution

24 months

Storage of the reconstituted product in vials

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Chemical and physical in-use stability has been demonstrated for 24 hours when stored at or below 25 °C or in the refrigerator at 2 °C to 8 °C prior to the preparation of the patient's infusion solution.

Storage of the diluted product for infusion

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Chemical and physical in-use stability has been demonstrated for 48 hours when stored in the refrigerator at 2 °C to 8 °C in the intravenous bag or bottle.

6.4 Special precautions for storage

Unopened vials: Store in the original packaging in a refrigerator (2 °C to 8 °C).

Do not freeze.

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

6.5 Nature and contents of container

IVECAS 50 IV and IVECAS 70 IV powder for concentrate for solution for infusion are supplied in clear glass type I, 10mL vials, sealed with a rubber stopper and an aluminium band with a plastic flip-off cap.

Supplied in packs of one 10 mL vial.

6.6 Special precautions for disposal and other handling

Reconstitution

DO NOT use any diluents containing dextrose (alpha-D-glucose), as IVECAS is not stable in such diluents.

DO NOT mix or co-infuse IVECAS with any other medicines. There is no data available on the compatibility of IVECAS with other intravenous substances, additives, or medicines. Visually inspect the infusion solution for particulate matter or discolouration before use.

Any unused medicine or waste material must be disposed of in accordance with local requirements.

INSTRUCTION FOR USE IN ADULTS

1. ***Reconstitution of vials***

To reconstitute the lyophilised powder, bring the refrigerated vial of IVECAS to room temperature and aseptically add 10,5 mL of sterile water for injection. The concentrations of the reconstituted vials will be: 7,2 mg/mL (70 mg vial) or 5,2 mg/mL (50 mg vial).

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

The reconstituted solution may be stored for up to 24 hours at or below 25 °C.

The reconstituted solution is clear and essentially free from visible particles.

2. Addition of reconstituted IVECAS to patient infusion solution

Diluents for the final solutions for infusion are sodium chloride 0,225 %; 0,45 % or 0,9 % m/v for injection, or lactated Ringer's solution.

The standard patient infusion is prepared by aseptically adding the appropriate amount of reconstituted medicines (see "Preparation of the patient infusion solutions") to a 250 mL intravenous bag or bottle. Reduced volume infusions in 100 mL may be used, if necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or if any precipitation is detected.

The prepared infusion solution must be used within 24 hours if stored at or below 25 °C or within 48 hours if refrigerated at 2 - 8 °C. IVECAS should be administered by slow intravenous infusion over approximately 1 hour.

Preparation of the patient infusion solutions in adults:

DOSE*	**Volume of reconstituted IVECAS for transfer to intravenous bag or bottle**	**Standard preparation (reconstituted IVECAS added to 250 mL) final concentration**	**Reduced volume infusion (reconstituted IVECAS added to 100 mL) final concentration**
70mg	10 mL	0,28 mg/mL	Not recommended
70mg (from two 50 mg vials)**	14 mL	0,28 mg/mL	Not recommended
50mg	10 mL	0,20 mg/mL	0,47 mg/mL
35 mg	5 mL	0,14 mg/mL	0,34 mg/mL

for moderate hepatic insufficiency (from one 70 mg vial)			
35mg for moderate hepatic insufficiency (from one 50 mg vial)	7 mL	0,14 mg/mL	0,34 mg/mL

* 10,5 mL should be used for reconstitution of all vials

**If a 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 BSA of the patient using the following formula (Mosteller formula)[1]:

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

[1] Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987 Oct 22;317(17): 1098 (letter)

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

1. Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation:

   BSA (m^2) X 70 mg/m^2 = Loading Dose

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

2. Equilibrate the refrigerated vial of IVECAS 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 (if using a 70 mg vial).
4. Remove the volume of medicinal product equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted IVECAS to an IV 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)[c] of reconstituted IVECAS 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 - 8°C.
5. If the calculated dose is less than 50 mg, then the dose may be prepared from the 50 mg vial (follow steps 2 - 4 from "***Preparation of the 50 mg/m^2 infusion for 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/m^2 infusion for paediatric patients >3 months of age (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:

   BSA (m^2) X 50 mg/m^2 = Daily Maintenance Dose

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

2. Equilibrate the refrigerated vial of IVECAS 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

(using a 50 mg vial).

4. Remove the volume of medicine equal to the calculated daily maintenance dose (Step 1) from the vial. Aseptically transfer this volume (mL)[c] of reconstituted IVECAS 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 IVECAS 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 - 8 °C.
5. If the actual daily maintenance dose is > 50 mg, then the dose may be prepared from the 70 mg vial (follow steps 2 - 4 from "***Preparation of the 70 mg/m^2 infusion for paediatric patients > 3 months of age (using a 70 mg vial)***"). The final caspofungin concentration in the 70 mg vial after reconstitution is 7,2 mg/mL.

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. IVECAS is formulated to provide the full labelled vial dose (50 mg or 70 mg) when 10 mL is withdrawn from the vial.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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