PROFESSIONAL INFORMATION
SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE
CASFIN 50 powder for concentrate for solution for infusion
CASFIN 70 powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
CASFIN 50: Each vial contains 50 mg caspofungin (as acetate).
CASFIN 70: Each vial contains 70 mg caspofungin (as acetate).
Contains sugar (sucrose 12,9 mg/ml and mannitol 8,6 mg/ml).
Each 50 mg vial contains 35,7 mg sucrose and 23,8 mg mannitol.
Each 70 mg vial contains 50,0 mg sucrose and 33,3 mg mannitol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Caspofungin 50 mg, 70 mg powder for concentrate for solution for infusion is a lyophilised sterile white to off-white powder to be reconstituted with water for injection and diluted prior to intravenous administration. After reconstitution: A clear solution free from visible particles. The pH 5,0 to 7,7

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
CASFIN is indicated in adults for:
- Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
- Treatment of invasive candidiasis, including candidemia.
- Treatment of oesophageal candidiasis where 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 CASFIN in paediatric patients 3 months to 17 years of age are supported by documented evidence. The efficacy and safety of CASFIN in neonate and infants under 3 months of age are not supported by adequate clinical studies. CASFIN has not been studied in paediatric patients with endocarditis, osteomyelitis and meningitis due to Candida. CASFIN has also not been studied as initial therapy for invasive aspergillosis in paediatric patients.

4.2 Posology and method of administration
General recommendation in adult patients
CASFIN should be administered in adults (≥ 18 years of age) by slow intravenous infusion over approximately 1 hour.

Posology
Empirical therapy
Adult patients: A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter.
Duration of treatment: 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 and 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, limited safety data suggest that an increase in dose to 70 mg daily is well tolerated.

Invasive candidiasis
Adult patients: A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter.
Duration of treatment: Duration of invasive candidiasis treatment should be based on 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. The safety and efficacy of multiple doses up to 150 mg daily (range: 1 to 51 days; median: 14 days) have been studied in adult patients with invasive candidiasis. CASFIN was generally well tolerated in these patients receiving CASFIN at this higher dose; however, the efficacy of CASFIN at this higher dose was generally similar to patients receiving the 50 mg daily dose of CASFIN.

Oesophageal and oropharyngeal candidiasis
Fifty (50) mg should be administered daily.

Invasive aspergillosis
Adult patients: A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. *Duration of treatment*: Duration of treatment should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. The efficacy of a 70 mg dose regimen in patients who are not clinically responding to the 50 mg daily dose 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.

Co-administration with metabolic inducers
A daily dose of 70 mg should be considered when CASFIN is co-administered with efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine (see section 4.5).

Special populations
No dosage adjustment is necessary based on gender or race (see section 5.2).
Elderly patients
In elderly patients (65 years of age or more), no dosage adjustment is necessary.
Renal impairment
No dosage adjustment is necessary based on renal impairment (see section 5.2).
Hepatic impairment
For adult patients with mild hepatic impairment (Child-Pugh score 5 to 6), no dosage adjustment is needed. For adult patients with moderate hepatic impairment (Child-Pugh score 7 to 9), 35 mg daily dose is recommended based upon pharmacokinetic data. However, where recommended an initial 70 mg loading dose should be administered on Day-1. There is no clinical experience in adult patients with severe hepatic impairment (Child-Pugh score greater than 9) and in paediatric patients with any degree of hepatic impairment (see section 4.4).

Paediatric population
Dosing in children and adolescents (3 months to 17 years of age) should be based on the patient's body surface area (see section 6.6, 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.
If the 50 mg/m^2 daily dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg). Although an increase in efficacy with 70 mg/m^2 daily has not been demonstrated, limited safety data suggest that an increase in dose to 70 mg/m^2 daily is well tolerated.
When CASFIN is co-administered to paediatric patients with metabolic inducers such as rifampin, efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine, use of a CASFIN dose of 70 mg/m^2 daily (not exceeding an actual daily dose of 70 mg) should be considered.

Method of administration
CASFIN should be administered by slow intravenous infusion over approximately 1 hour. For reconstitution directions and instructions for use see section 6.6. Both 50 mg and 70 mg vials are available. CASFIN should be given as a single daily infusion.
[1] Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987 Oct 22;317(17):1098 (letter)

4.3 Contraindications
- Hypersensitivity to caspofungin or to any of the excipients of CASFIN (see section 6.1)
- Severe hepatic insufficiency as efficacy and safety has not been studied.

4.4 Special warnings and precautions for use
Hypersensitivity reactions
Anaphylaxis has been reported during administration of CASFIN. If this occurs, CASFIN 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.

Non-Candida yeasts and non-Aspergillus moulds
Limited data suggest that less common non-Candida yeasts and non-Aspergillus moulds are not covered by CASFIN. The efficacy of CASFIN against these fungal pathogens has not been established.

Concomitant use with ciclosporin
Data on concomitant use of CASFIN with two 3 mg/kg doses of ciclosporin 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 treatment. There is an increase of approximately 35 % in the area under the curve (AUC) of caspofungin, therefore, close monitoring of liver enzymes should be considered if CASFIN and ciclosporin are used concomitantly. Blood levels of ciclosporin remained unchanged.

Hepatic impairment
In adult patients with mild and moderate hepatic impairment, the AUC is increased about 20 % and 75 %, respectively. A reduction of the daily dose to 35 mg is recommended for adults with moderate hepatic impairment. There is no clinical experience in adults with severe hepatic impairment or in paediatric patients with any degree of hepatic impairment. A higher exposure than in moderate hepatic impairment is expected and caspofungin should be used with caution in these patients (see sections 4.2 and 5.2).

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

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

Contains sucrose
CASFIN contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take CASFIN.

4.5 Interaction with other medicines and other forms of interaction
Data indicate that caspofungin is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. It is documented that caspofungin does not induce the CYP3A4 metabolism of other substances. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

Ciclosporin
It is documented that ciclosporin (one 4 mg/kg dose or two 3 mg/kg doses 12 hours apart) increased the AUC of caspofungin by approximately 35 %. These AUC increases are probably due to reduced uptake of caspofungin by the liver. CASFIN did not increase the plasma levels of ciclosporin. There were transient increases in liver ALT and AST of less than or equal to 3-fold the upper limit of normal (ULN) when CASFIN and ciclosporin were co-administered, that resolved with discontinuation of CASFIN. In a retrospective study of 40 patients treated during marketed use with caspofungin and ciclosporin for 1 to 290 days (median 17,5 days), no serious hepatic adverse reactions were noted (see section 4.4). Close monitoring of liver enzymes should be considered if the two medicines are used concomitantly.

Tacrolimus
CASFIN reduced the 12-hour blood concentration of tacrolimus by 26 % in healthy adult volunteers. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are mandatory.

Other medicines
Data show that the pharmacokinetics of caspofungin, as in CASFIN, are not altered by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus. CASFIN did not influence the pharmacokinetics of amphotericin B, itraconazole, rifampicin or mycophenolate mofetil.

Rifampicin and other medicines that induce metabolic enzymes
Results from clinical interaction studies indicate that rifampicin both induces and inhibits caspofungin disposition with net induction at steady state. In addition, results from population pharmacokinetic screening in adults suggests that co-administration of other inducers of medicine clearance (efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine) with CASFIN 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 CASFIN 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 CASFIN should be considered (see section 4.2).

Amphotericin B
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.

Paediatric population
In paediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with CASFIN may result in clinically meaningful reductions in caspofungin, as in CASFIN, trough concentrations. This finding may indicate that paediatric patients will have similar reductions with inducers as seen in adults. When CASFIN is co-administered to paediatric patients (12 months to 17 years of age) with inducers of medicines clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, an increase in the daily dose of CASFIN should be considered (see section 4.2).

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no or limited data from the use of CASFIN in pregnant women. CASFIN should not be used during pregnancy.
Breastfeeding
It is unknown whether caspofungin is excreted in human milk. Women receiving CASFIN should not breastfeed their infants.
Fertility
For caspofungin, there were no effects on fertility in studies conducted in male and female rats. There are no clinical data for caspofungin to assess its impact on fertility.

4.7 Effects on ability to drive and use machines
No data are available on whether CASFIN has an influence on the ability to drive and use machines. Patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience adverse symptoms (see section 4.8).

4.8 Undesirable effects
a. 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.
Phlebitis was a frequently 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 were typically mild and less frequently led to discontinuation.

b. Tabulated summary of adverse reactions
The following adverse reactions were reported during clinical studies and/or post-marketing use:

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Decreased haemoglobin, decreased haematocrit, decreased white blood cell count, anaemia
	Less frequent	Thrombocytopenia, coagulopathy, leukopenia, increased eosinophil count, decreased platelet count, increased platelet count, decreased lymphocyte count, increased white blood cell count, decreased neutrophil count
Metabolism and nutrition disorders	Frequent	Hypokalemia
	Less frequent	Fluid overload, hypomagnesaemia, anorexia, electrolyte imbalance, hyperglycaemia, hypocalcaemia, metabolic acidosis
Psychiatric disorders	Less frequent	Anxiety, disorientation, insomnia
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, dysgeusia, paraesthesia, somnolence, tremor, hypoesthesia
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	Phlebitis, thrombophlebitis
	Less frequent	Flushing, hot flush, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
	Less frequent	Nasal congestion, pharyngolaryngeal pain, tachypnoea, bronchospasm, cough, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, vomiting
	Less frequent	Abdominal pain, upper abdominal pain, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia, flatulence
Hepato-biliary disorders	Frequent	Elevated liver values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, bilirubin conjugated, blood bilirubin)
	Less frequent	Cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, abnormal hepatic function, hepatotoxicity, liver disorder, increased gamma-glutamyl transferase
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, erythema, hyperhidrosis
	Less frequent	Multiforme erythema, 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
Musculoskeletal and connective tissue 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 administration site conditions	Frequent	Pyrexia, chills, infusion-site pruritus
	Less frequent	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	Elevated liver test values (aspartate transaminase (AST)), alanine transaminase (ALT), alkaline phosphatase, direct and total bilirubin) decreased haemoglobin, decreased haematocrit, low potassium, low albumin, decreased white blood cells
	Less frequent	Increased blood creatinine, red blood cells urine positive, decreased total protein, protein urine present, prolonged prothrombin time, shortened prothrombin time, decreased blood sodium increased blood sodium, decreased blood calcium, increased blood calcium, decreased blood chloride, blood glucose increased, decreased blood magnesium, decreased blood phosphorus, increased blood phosphorus, increased blood urea, prolonged activated partial thromboplastin time, decreased blood bicarbonate, increased blood chloride, increased blood potassium, increased blood pressure, decreased blood uric acid, blood urine present, abnormal breath sounds, decreased carbon dioxide, increased immunosuppressant medicine level, increased international normalised ratio, urinary casts, white blood cells urine positive, and increased urine pH

Paediatric patients
The most common adverse experiences reported in paediatric patients treated with CASFIN were pyrexia, rash and headache.

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Increased eosinophil count
Nervous system disorders	Frequent	Headache
Cardiac disorders	Frequent	Tachycardia
Vascular disorders	Frequent	Flushing, hypotension
Hepato-biliary 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	Elevated liver enzyme levels (AST, ALT), decreased potassium, hypomagnesemia, increased glucose, decreased phosphorus, and increased phosphorus, increased eosinophils.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
A dose of 210 mg, administered as a single dose to adult healthy subjects, was generally well tolerated. In addition, a dose of 150 mg once daily up to 51 days administered to adult patients was generally well tolerated.
Inadvertent administration of up to 400 mg of caspofungin in one day has been reported. These occurrences did not result in clinically important adverse reactions. Caspofungin is not dialysable.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antimycotics for systemic use ATC Code: J02AX04
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 yeast. Beta (1,3)-D-glucan is not present in mammalian cells.

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.

Mechanism of resistance
Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment. MIG (minimum inhibitory concentration) values for caspofungin should not be used to predict clinical outcome, since a correlation between MIG values and clinical outcome has not been established.

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 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 gamma-phase also occurs (half-life 40 to 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 [^{3}H] caspofungin acetate. 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 and undergoes spontaneous chemical degradation to an open-ring peptide compound. At later time points, there is a low level of covalent binding of radio-label in plasma following single-dose administration of [^{3}H] caspofungin acetate, which may be due to two reactive intermediates formed during the chemical degradation of caspofungin. Additional metabolism involves hydrolysis into constitutive amino acids and their derivatives, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine. These two tyrosine derivatives are found only in urine, suggesting rapid clearance of these derivatives by the kidneys.

Elimination
In single-dose radio-labelled pharmacokinetic studies plasma, urine and faeces were collected over 27 days, or 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 radio-label fell below the limit of quantitation at 22,3 weeks post-dose. Renal clearance of parent substance is low (approximately 0,15 ml/min). A small amount of caspofungin is excreted unchanged in urine (approximately 1,4 % of dose).

Linearity/non-linearity
Caspofungin displays moderate non-linear pharmacokinetics with increased accumulation as the dose is increased, and a dose dependency in the time to reach steady state upon multiple-dose administration.

Special populations
Weight: Weight was found to influence caspofungin pharmacokinetics in the population pharmacokinetic analysis in adult candidiasis patients. The plasma concentrations decrease with increasing weight. The average exposure in an adult patient weighing 80 kg was predicted to be about 23 % lower than in an adult patient weighing 60 kg.
Hepatic impairment: In adult patients with mild and moderate hepatic impairment, the AUC is increased about 20 and 75 %, respectively. There is no clinical experience in adult patients with severe hepatic impairment and in paediatric patients with any degree of hepatic impairment. In a multiple-dose study, a dose reduction of the daily dose to 35 mg in adult patients with moderate hepatic impairment has been shown to provide an AUC similar to that obtained in adult subjects with normal hepatic function receiving the standard regimen (see section 4.2).
Renal impairment: In a clinical study of single 70 mg doses, caspofungin pharmacokinetics were similar in adult volunteers with mild renal impairment (creatinine clearance 50 to 80 ml/min) and control subjects. Moderate (creatinine clearance 31 to 49 ml/min), advanced (creatinine clearance 5 to 30 ml/min), and end-stage (creatinine clearance <10 ml/min and dialysis dependent) renal impairment moderately increased caspofungin plasma concentrations after single-dose administration (range: 30 to 49 % for AUC). However, in adult patients with invasive candidiasis, oesophageal candidiasis, or invasive aspergillosis who received multiple daily doses of caspofungin 50 mg, there was no significant effect of mild to advanced renal impairment on caspofungin concentrations. No dosage adjustment is necessary for patients with renal impairment. Caspofungin is not dialysable, thus supplementary dosing is not required following haemodialysis.
Gender : Caspofungin plasma concentrations were on average 17 to 38 % higher in women than in men.
Elderly: A modest increase in AUC (28 %) and C_{24h} (32 %) was observed in elderly male subjects compared with young male subjects. 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.

Paediatric population
In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ is generally comparable to that seen in adults receiving caspofungin at 50 mg daily.
In children (ages 2 to 11 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses is comparable to that seen in adults receiving caspofungin at 50 mg/day.
In young children and toddlers (ages 12 to 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses is comparable to that seen in adults receiving caspofungin at 50 mg daily and to that in older children (2 to 11 years of age) receiving the 50 mg/m^2 daily dose.
Overall, the available pharmacokinetic, efficacy, and safety data are limited in patients 3 to 10 months of age.-
In neonates and infants (< 3 months) receiving caspofungin at 25 mg/m^2 daily (corresponding mean daily dose of 2,1 mg/kg), caspofungin peak concentration ($C_{1\ hr}$) and caspofungin trough concentration ($C_{24\ hr}$) after multiple doses are comparable to that seen in adults receiving caspofungin at 50 mg daily. The efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sucrose, Mannitol (E421), Carbon dioxide (E290) (pH adjustment), Hydrochloric acid, concentrate (E507) (pH adjustment), Sodium hydroxide (E524) (pH adjustment), Water for injection.

6.2 Incompatibilities
Do not mix with diluents containing dextrose, as CASFIN is not stable in diluents containing dextrose. In the absence of compatibility studies, CASFIN must not be mixed with other medicines.

6.3 Shelf life
36 months (stored at 2 ºC to 8 ºC). After reconstitution, CASFIN 50 and 70 powder for concentrate for solution for infusion may be stored for up to 24 hours at or below 25 ºC. Stability data have shown that CASFIN 50 and 70 powder for concentrate for solution for infusion can be used within 24 hours when stored at 25 ºC or less, or within 48 hours when the intravenous infusion bag (bottle) is stored refrigerated (2 °C to 8 ºC) and 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. CASFIN contains no preservatives. From a microbiological point of view, CASFIN 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 °C 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 to 8 °C).
For storage conditions after reconstitution and dilution of CASFIN, see section 6.3.

6.5 Nature and contents of container
CASFIN 50: 10 ml glass vial with a rubber stopper and an aluminium seal with a red plastic flip-off cap.
CASFIN 70: 10 ml glass vial with a rubber stopper and an aluminium seal with an orange plastic flip-off cap.
A single vial is packed in an outer carton.

6.6 Special precautions for disposal and other handling
Reconstitution of CASFIN
DO NOT USE ANY DILUENTS CONTAINING DEXTROSE
CASFIN is not stable in diluents containing dextrose.
DO NOT MIX OR CO-INFUSE CASFIN WITH ANY OTHER MEDICINES
There is no data available on the compatibility of CASFIN with other intravenous substances, additives or medicines. Visually inspect the infusion solution for particulate matter or discolouration. Do not use the solution if the solution is cloudy or has precipitated. CASFIN is formulated to provide the full labelled vial dose (50 mg or 70 mg) when 10 ml is withdrawn from the vial.

Instructions for use in adults
Step 1: Reconstitution of vials
To reconstitute the powdered medicine, bring the refrigerated vial of CASFIN to room temperature and aseptically add 10,5 ml 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. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.

Step 2: Addition of Reconstituted CASFIN 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 CASFIN (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 has 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. CASFIN should be administered by slow intravenous infusion over approximately 1 hour.

Preparation of the patient infusion solutions in adults

DOSE*	Volume of reconstituted CASFIN for transfer to intravenous bag or bottle	Standard preparation (reconstituted CASFIN added to 250 ml) final concentration	Reduced volume infusion (reconstituted CASFIN 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
35 mg 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 body surface area (BSA) of the patient using the following formula (Mosteller Formula):

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

Preparation of the 70 mg/m^2 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 CASFIN to room temperature.
3. Aseptically add 10,5 ml of Sterile Water for Injection. This reconstituted solution may be stored for up to 24 hours at 25 °C. 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) of reconstituted CASFIN 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) of reconstituted CASFIN can be added to a reduced volume of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection, not to exceed a final concentration of 0,5 mg/ml. This infusion solution must be used within 24 hours if stored at or below 25 °C or within 48 hours if stored refrigerated at 2 to 8 °C.
5. If the calculated loading dose is less than 50 mg, then the dose may be prepared from the 50 mg vial [follow Steps 2 to 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/m^2 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) 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 CASFIN to room temperature.
3. Aseptically add 10,5 ml of Sterile Water for Injection. This reconstituted solution may be stored for up to 24 hours at 25 °C. This will give a final caspofungin concentration in the vial of 5,2 mg/ml.
4. Remove the volume of CASFIN equal to the calculated daily maintenance dose (Step 1) from the vial.
5. Aseptically transfer this volume (ml) of reconstituted CASFIN 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) of reconstituted CASFIN 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.
6. If the actual daily maintenance dose is > 50 mg, then the dose may be prepared from the 70 mg vial [follow Steps 2 to 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.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Kahma Biotech (Pty) Ltd. 106, 16th Road, Midrand.

8 REGISTRATION NUMBERS
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10 DATE OF REVISION OF THE TEXT
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