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/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.
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 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/m² 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_{last} (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/m² 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/m² 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/m² 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/m² 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/m² 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 °C to 8 °C). 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 °C. 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 °C or less, or within 48 hours when the intravenous infusion bag (bottle) is stored refrigerated (2 °C to 8 °C) 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/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 (m²) X 70 mg/m² = 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/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 (m²) X 50 mg/m² = 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
CASFIN 50: 55/20.2.2/0236
CASFIN 70: 55/20.2.2/0237

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
7 June 2022

10 DATE OF REVISION OF THE TEXT
N.A

L12276 E/22

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Dimensions: 310 x 570 ± 2 mm
Font Style: Helvetica Neue LT Com
Font Size: 6 pt
Text matter print both sides on Bible Paper with 3 columns.

570 mm

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S4

1 NAAM VAN DIE MEDISYNE
CASFIN 50 poeier vir konsentraat vir oplossing vir infusie
CASFIN 70 poeier vir konsentraat vir oplossing vir infusie

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
CASFIN 50
Elke flessie bevat 50 mg kaspofungien (as asetaat).
CASFIN 70
Elke flessie bevat 70 mg kaspofungien (as asetaat).
Bevat suiker (sukrose 12,9 mg/ml en mannitol 8,6 mg/ml).
Elke 50 mg flessie bevat 35,7 mg sukrose en 23,8 mg mannitol.
Elke 70 mg flessie bevat 50,0 mg sukrose en 33,3 mg mannitol.
Vir die volledige lys van bestanddele, sien afdeling 6.1

3 FARMASEUTIESE VORM
Kaspofungien 50 mg, 70 mg poeier vir konsentraat vir oplossing vir infusie is 'n vriesgedroogde, steriele wit tot naaswit poeier om hersaamgestel te word met water vir inspuiting en verdun te word voor intraveneuse toediening.
Na hersamestelling: 'n Deursigtige oplossing, vry van sigbare deeltjies.
Die pH 5,0 tot 7,7.

4 KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
CASFIN is aangedui in volwassenes vir:
- Empiriese behandeling vir vermoedelike fungus infeksies in febriele, neutropeniese pasiënte.
- Behandeling van indringende kandidiase, insluitend kandidemie.
- Behandeling van esofagus kandidiase waar IV anti-fungus behandeling toepaslik is.
- Behandeling van orofaringeale kandidiase waar IV anti-fungus behandeling toepaslik is.
- Behandeling van indringende aspergillose in pasiënte wat weerstandbiedend is tot, of onverdraagsaam is vir ander behandeling, insluitend amfoterisien B, lipiedformulerings van amfoterisien B en itrakonasool.

Pediatriese gebruik
Die veiligheid en effektiwiteit van CASFIN in pediatriese pasiënte van 3 maande tot 17 jaar oud word ondersteun deur gedokumenteerde bewyse.
Die effektiwiteit en veiligheid van CASFIN in pasgebore babas en babas jonger as 3 maande oud, word nie deur voldoende kliniese studies ondersteun nie.
CASFIN is nie bestudeer in pediatriese pasiënte met endokarditis, osteomiëlitis en meningitis as gevolg van Candida nie. CASFIN is ook nie bestudeer as aanvangsbehandeling vir indringende aspergillose in pediatriese pasiënte nie.

4.2 Posologie en metode van toediening
Algemene aanbeveling in volwasse pasiënte
CASFIN moet toegedien word by volwassenes (≥ 18 jaar oud) deur stadige intraveneuse infusie oor ongeveer 1 uur.
Posologie:
Empiriese terapie
Volwasse pasiënte: 'n Enkel, 70 mg ladingsdosis moet op Dag 1 toegedien word, gevolg deur 50 mg daarna**.**
Duur van behandeling: Die duur van die behandeling moet gebaseer word op die kliniese reaksie van die pasiënt. Empiriese behandeling moet voortgesit word totdat neutropenie opgeklaar is. Pasiënte wat gevind is om 'n fungus infeksie te hê, moet vir 'n minimum van 14 dae behandel word en die behandeling moet vir ten minste 7 dae voortduur nadat beide neutropenie en kliniese simptome opgeklaar is. Indien die 50 mg goed verdra word, maar nie 'n voldoende kliniese reaksie lewer nie, kan die daaglikse dosering verhoog word tot 70 mg. Alhoewel 'n toename in effektiwiteit met 70 mg per dag nie aangetoon is nie, dui beperkte veiligheidsdata daarop dat 'n toename in dosering tot 70 mg per dag, goed verdra word.

Indringende kandidiase
Volwasse pasiënte: 'n Enkel, 70 mg ladingsdosis moet op Dag 1 toegedien word, gevolg deur 50 mg daarna.
Duur van die behandeling: Die duur van behandeling van indringende kandidiase moet gebaseer word op die kliniese- en mikrobiologiese reaksie van die pasiënt. Oor die algemeen moet fungus infeksie behandeling voortduur vir ten minste 14 dae na die laaste positiewe kultuur. Pasiënte wat aanhoudend neutropenies bly, kan 'n langer behandelingskursus regverdig afhangende van die opklaring van die neutropenie.
Die veiligheid en effektiwiteit van meervoudige doserings tot en met 150 mg per dag (wykreidte: 1 tot 51 dae; mediaan: 14 dae) is bestudeer in volwasse pasiënte met indringende kandidiase. CASFIN was oor die algemeen goed verdra in hierdie pasiënte wat CASFIN teen hierdie hoër dosering ontvang het; die effektiwiteit van CASFIN by hierdie hoër dosering was egter oor die algemeen soortgelyk aan die van pasiënte wat die daaglikse 50 mg dosering van CASFIN ontvang het.

Esofagus- en orofaringeale kandidiase
Vyftig (50) mg moet daagliks toegedien word.

Indringende aspergillose
Volwasse pasiënte: 'n Enkel 70 mg ladingsdosis moet op Dag 1 toegedien word, gevolg deur 50 mg daagliks daarna. *Duur van behandeling*: Duur van behandeling moet gebaseer wees op die erns van die pasiënt se onderliggende siekte, herstel van immuunonderdrukking en kliniese reaksie. Die effektiwiteit van 'n 70 mg dosis regime in pasiënte wat nie klinies reageer op die 50 mg daaglikse dosis nie, is nie bekend nie. Veiligheidsdata dui daarop dat 'n toename in dosering tot 70 mg per dag, goed verdra word. Die effektiwiteit van doserings bo 70 mg is nie voldoende bestudeer in pasiënte met indringende aspergillose nie.

Gelyktydige toediening met metaboliese induseerders
'n Daaglikse dosis van 70 mg moet oorweeg word wanneer CASFIN saam met efavirens, nevirapien, rifampisien, deksametasoon, fenitoïen of karbamasepien toegedien word (sien afdeling 4.5).

Spesiale populasies
Geen dosisaanpassing, is nodig gebaseer op geslag of ras nie (sien afdeling 5.2).
Bejaarde pasiënte
In bejaarde pasiënte (65 jaar oud of ouer) is geen dosisaanpassing nodig nie.
Renale inkorting
Geen dosisaanpassing is nodig gebaseer op renale inkorting nie (sien afdeling 5.2).

Hepatiese inkoring
Vir volwasse pasiënte met ligte hepatiese inkorting (Child-Pugh-telling 5 tot 6) is geen dosisaanpassing nodig nie. Vir volwasse pasiënte met matige hepatiese inkorting (Child-Pugh-telling 7 tot 9) word daaglikse dosisse van 35 mg aanbeveel, gebaseer op farmakokinetiese data. Waar aanbeveel, moet 'n aanvanklike ladingsdosis van 70 mg egter op Dag-1 toegedien word. Daar is geen kliniese ondervinding in volwasse pasiënte met 'n ernstige hepatiese inkorting, (Child-Pugh-telling groter as 9) en in pediatriese pasiënte met enige graad van hepatiese inkorting nie (sien afdeling 4.4).

Pediatriese populasie
Dosering in kinders en adolessente (3 maande tot 17 jaar oud) moet gebaseer word op die pasiënt se liggaamsoppervlakarea (sien afdeling 6.6, Gebruiksaanwysings vir gebruik in Pediatriese Pasiënte, Mosteller[1]-Formule).
Vir alle indikasies moet 'n enkel 70 mg/m² ladingsdosis (om nie 'n werklike daaglikse dosis van 70 mg te oorskry nie) op Dag 1 toegedien word, gevolg deur 50 mg/m² daarna (om nie 'n werklike daaglikse dosis van 70 mg te oorskry nie).
Duur van die behandeling moet volgens die indikasie geïndividualiseer word, soos beskryf vir elke indikasie in volwassenes.
Indien die daaglikse dosis van 50 mg/m² goed verdra word, maar nie voldoende kliniese reaksie lewer nie, kan die daaglikse dosis verhoog word tot 70 mg/m² (moet nie 'n werklike daaglikse dosis van 70 mg oorskry nie). Alhoewel 'n toename in effektiwiteit met 70 mg/m² per dag nie aangetoon is nie, dui beperkte veiligheidsdata daarop dat 'n toename in dosering tot 70 mg/m² per dag goed verdra is.
Wanneer CASFIN gelyktydig met metaboliese induseerders soos rifampien, efavirens, nevirapien, fenitoïen, deksametasoon of karbamasepien, toegedien word aan pediatriese pasiënte, moet gebruik van 'n CASFIN dosering van 70 mg/m² per dag (moet nie die werklike daaglikse dosering van 70 mg oorskry nie) oorweeg word

Metode van toediening
CASFIN moet toegedien word deur stadige intraveneuse infusie oor ongeveer 1 uur. Vir hersamestellingsriglyne en gebruiksaanwysings, sien afdeling 6.6.
Beide 50 mg en 70 mg flessies is beskikbaar.
CASFIN moet as 'n enkel daaglikse infusie gegee word.
[1]*Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987 Oct 22;317(17):1098 (letter).*

4.3 Kontraindikasies
- Hipersensitiwiteit vir kaspofungien of vir enige van die onaktiewe bestanddele van CASFIN (sien afdeling 6.1)
- Ernstige hepatiese inkorting, aangesien effektiwiteit en veiligheid nie bestudeer is nie.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Hipersensitiwiteits reaksies
Anafilakse is aangemeld tydens toediening van CASFIN. Indien dit gebeur, moet CASFIN gestaak word en toepaslike behandeling toegedien word. Moontlike histamien-gemedieerde ongunstige reaksies, insluitend veluitslag, swelling van die gesig, angioëdeem, pruritus, gevoel van warmte, of brongospasma is aangemeld en mag staking en/of toediening van toepaslike behandeling vereis.

Nie-Candida-giste en nie-Aspergillus-swamme
Beperkte data dui daarop dat minder algemene nie-*Candida*-giste en nie-*Aspergillus*-swamme, nie deur CASFIN gedek word nie. Die effektiwiteit van CASFIN teen hierdie fungus patogene is nie vasgestel nie.

Gelyktydige gebruik met siklosporien
Data oor die gesamentlike gebruik van CASFIN met twee, 3 mg/kg doserings van siklosporien, het verbygaande verhogings in alanientransaminase (ALT) en aspartaattransaminase (AST) van minder as, of gelyk aan, 3-voudig die boonste limiet van normaal (BLN) getoon, wat met staking van die behandeling opgeklaar het. Daar is 'n toename van ongeveer 35 % in die area onder die kurwe (AOK) van kaspofungien, daarom moet oukeurige monitering van lewerensieme oorweeg word indien CASFIN en siklosporien gelyktydige gebruik word. Bloedvlakke van siklosporien het onveranderd gebly.

Hepatiese inkorting
In volwasse pasiënte met ligte en matige hepatiese inkorting, verhoog die AOK onderskeidelik ongeveer 20 % en 75 %. 'n Vermindering van die daaglikse dosis tot 35 mg, word aanbeveel vir volwassenes met matige hepatiese inkorting. Daar is geen kliniese ondervinding in volwassenes met ernstige hepatiese inkorting of in pediatriese pasiënte met enige graad van hepatiese inkorting nie. 'n Hoër blootstelling word verwag as in matige hepatiese inkorting, en kaspofungien moet met versigtigheid in hierdie pasiënte gebruik word (sien afdelings 4.2 en 5.2).

Lewerfunksie toetse
Laboratoriumafwykings in lewerfunksietoetse is gesien in gesonde vrywilligers en volwassenes en pediatriese pasiënte wat met CASFIN behandel is. In sommige volwasse- en pediatriese pasiënte met ernstige onderliggende toestande wat veelvuldige gelyktydige middels saam met CASFIN ontvang het, is gevalle van kliniese beduidende hepatiese disfunksie, hepatitis en lewerversaking aangemeld; 'n oorsaaklike verband met CASFIN is nie vasgestel nie. Pasiënte wat abnormale lewerfunksietoetse ontwikkel tydens behadeling met CASFIN, moet gemonitor word vir bewyse van verswakkende hepatiese funksie en die risiko/voordeel van voortgesette CASFIN behandeling moet geherevalueer word.

Allergiese velreaksies
Gevalle van Stevens-Johnson-sindroom (SJS) en toksiese epidermale nekrolise (TEN), is aangemeld met die na-bemarking gebruik van CASFIN. Versigtigheid moet toegepas word in pasiënte met 'n geskiedenis van allergiese velreaksies (sien afdeling 4.8).

Bevat sukrose
CASFIN bevat sukrose wat 'n effek op die glukemiese beheer van pasiënte met diabetes mellitus kan hê. Pasiënte met seldsame oorerflike toestande soos fruktose-onverdraagsaamheid, glukose-galaktose wanabsorpsie of sukrase-isomaltase ontoereikendheid, moet nie CASFIN gebruik nie.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Data dui aan dat kaspofungien nie 'n inhibeerder van enige ensiem in die sitochroom P450 (SIP) stelsel is nie. Dit is gedokumenteer dat kaspofungien nie die SIP3A4 metabolisme van ander stowwe induseer nie. Kaspofungien is nie 'n substraat vir P-glikoproteïen nie, en is 'n swak substraat vir sitochroom P450 ensieme.

Siklosporien
Dit is gedokumenteer dat siklosporien (een dosering van 4 mg/kg of twee doserings van 3 mg/kg 12 uur uitmekaar) die AOK van kaspofungien met ongeveer 35 % verhoog het. Hierdie AOK -verhogings is waarskynlik te wyte aan die verminderde opname van kaspofungien deur die lewer. CASFIN het nie die plasmavlakke van siklosporien verhoog nie. Daar was kortstondige toenames in lewer-ALT en AST van minder as of gelyk aan 3-voudig die boonste limiet van normaal (BLN) wanneer CASFIN en siklosporien gelyktydig toegedien is, wat opgeklaar het met die staking van CASFIN. In 'n retrospektiewe studie van 40 pasiënte wat behandel is tydens bemarkingsgebruik met kaspofungien en siklosporien vir 1 tot 290 dae (mediaan 17,5 dae), is geen ernstige hepatiese ongunstige reaksies aangeteken nie (sien afdeling 4.4). Noukeurige monitering van lewerensieme moet oorweeg word indien die twee medisynes gelyktydig gebruik word.

Takrolimus
CASFIN verminder die 12-uur bloedkonsentrasie van takrolimus met 26 % in gesonde volwasse vrywilligers. Vir pasiënte wat beide behandelings ontvang, is standaardmonitering van takrolimus bloedkonsentrasies en toepaslike dosisaanpassings van takrolimus verpligtend.

Ander medisyne
Data toon dat die farmakokinetika van kaspofungien, soos in CASFIN, nie verander word deur itrakonasool, amfoterisien-B, mikofenolaat, nelfinavir of takrolimus nie. CASFIN het nie die farmakokinetika van amfoterisien-B, itrakonasool, rifampisien of mikofenolaatmofetiel beïnvloed nie.

Rifampisien en ander medisyne wat metaboliese ensieme induseer
Resultate van kliniese interaksie studies dui aan dat rifampisien beide die kaspofungien ingesteldheid induseer en inhibeer, met netto induksie by gelykvlak. Boonop dui die resultate van populasie farmakokinetiese ondersoek in volwassenes aan dat gelyktydige toediening van ander geneesmiddel opruimingsinduseerdes (efavirens, nevirapien, fenitoïen, deksametasoon of karbamasepien) met CASFIN ook klinies betekenisvolle verlagings in kaspofungien konsentrasies kan veroorsaak. Beskikbare data dui daarop dat die induseerbare geneesmiddel opruimingsmeganisme wat betrokke is in kaspofungien disposisie, waarskynlik 'n opname vervoerproses is, eerder as metabolisme. Wanneer CASFIN dus gelyktydig saam met induseerders van geneesmiddelopruiming, soos efavirens, nevirapien, rifampisien, deksametasoon, fenitoïen of karbamasepien aan volwasse pasiënte toegedien word, moet die daaglikse dosis van 70 mg CASFIN oorweeg word (sien afdeling 4.2).

Amfoterisien B
In vitro en *in vivo* studies van kaspofungien asetaat, in kombinasie met amfoterisien B, toon geen antagonisme van antifungus aktiwiteit teen of *A. fumigatus* of *C. albicans* nie. Resultate van *in vitro* studies dui daarop dat daar bewyse was van toevoeging/onverskillige of sinergistiese aktiwiteit teen *A. fumigatus* en toevoeging/onverskillige aktiwiteit teen *C. albicans*. Die kliniese betekenis van hierdie resultate is onbekend.

Pediatriese populasie
In pediatriese pasiënte dui die resultate van regressie ontleding van farmakokinetiese data aan dat gelyktydige toediening van deksametasoon met CASFIN klinies betekenisvolle verlagings in kaspofungien, soos in CASFIN, kan veroorsaak, trog konsentrasies. Hierdie bevinding kan daarop dui dat pediatriese pasiënte soortgelyke verminderings met induseerders sal hê as gesien in volwassenes. Wanneer CASFIN gelyktydig toegedien word aan pediatriese pasiënte (12 maande tot 17 jaar oud) met induseerders van medisyne, soos rifampisien, efavirens, nevirapien, fenitoïen, deksametasoon of karbamasepien, moet 'n verhoging in die daaglikse dosering van CASFIN oorweeg word (sien afdeling 4.2)

4.6 Fertiliteit, swangerskap en laktasie
Swangerskap
Daar is geen, of beperkte inligting oor die gebruik van CASFIN in swanger vrouens. CASFIN moet nie tydens swangerskap gebruik word nie.
Borsvoeding
Die is onbekend of kaspofungien in menslike melk uitgeskei word. Vrouens wat CASFIN ontvang, moet nie hul babas borsvoed nie.
Fertiliteit
Vir kaspofungien was daar geen effekte op vrugbaarheid in studies wat uitgevoer is in manlike en vroulike rotte nie. Daar is geen kliniese data vir kaspofungien om die impak daarvan op fertiliteit te bepaal nie.

4.7 Effekte op vermoë om te bestuur en gebruik van masjiene
Daar is geen data beskikbaar oor of CASFIN 'n invloed het op die vermoë om te bestuur en om masjiene te gebruik nie. Pasiënte moet versigtig wees wanneer hulle bestuur of masjinerie gebruik en moet aangeraai word om nie te bestuur of masjinerie te gebruik indien hulle ongewenste simptome ondervind nie (sien afdeling 4.8).

4.8 Ongewenste effekte
a. Opsomming van die veiligheidsprofiel
Hipersensitiwiteitsreaksies (anafilakse en moontlik histamienbemiddelde ongunstige reaksies) is aangemeld (sien afdeling 4.4).
In pasiënte met indringende aspergillose is pulmonale edeem, volwasse respiratoriese noodsindroom (VRNS) en radiografiese infiltrate, ook aangemeld.
Flebitis was 'n gereelde aangemelde lokale ongunstige reaksie by die inspuitplek in alle pasiëntpopulasies gewees. Ander lokale reaksies het eriteem, pyn/ teerheid, jeuk, afskeiding en 'n brandende sensasie ingesluit.
Aangemelde kliniese en laboratoriumafwykings onder alle volwassenes was tipies lig en het minder gereeld tot staking gelei.

b. Opsomming van nadelige reaksies in tabelvorm
Die volgende nadelige reaksies is aangemeld tydens kliniese studies, en/of na bemarkingsgebruik:

MedDRA Sisteem Orgaan Klas	Frekwensie	Newe effekte
Bloed- en limfstelselversteurings	Gereeld	Verminderde hemoglobien, verminderde hematokrit, verminderde witbloedseltelling, anemie
	Minder gereeld	Trombositopenie, koagulopatie, leukopenie, verhoogde eosinofieltelling, verlaagde bloedplaatjietelling, verhoogde bloedplaatjietelling, verminderde limfosiettelling, verhoogde witbloedseltelling, verminderde neutrofieltelling
Metabolisme en voedingsversteurings	Gereeld	Hipokalemie
	Minder gereeld	Vloeistofoorlading, hipomagnesemie, anoreksie, elektrolietwanbalans, hiperglukemie, hipokalsemie, metaboliese asidose
Psigiatriese versteurings	Minder gereeld	Angstigheid, disoriëntasie, slaaploosheid
Senuweestelsel versteurings	Gereeld	Hoofpyn
	Minder gereeld	Duiseligheid, disgeusie, parestesie, slaperigheid, bewing, hipoëstesie
Oog versteurings	Minder gereeld	Okulêre ikterus, dowwe visie, ooglidedeem, verhoogde lakrimasie
Kardiale versteurings	Minder gereeld	Palpitasies, tagikardie, disritmieë, arteriale fibrillasie, kongestiewe hartversaking
Vaskulêre versteurings	Gereeld	Flebitis, tromboflebitis
	Minder gereeld	Blosing, warm gloed, hipertensie hipotensie
Respiratoriese, torakale en mediastinale versteurings	Gereeld	Dispnee
	Minder gereeld	Neuskongestie, faringolaringeale pyn, tagipnee, brongospasma, hoes, dispnee, nagtelike paroksimale, hipoksie, geraas, gehyg
Gastroïntestinale versteurings	Gereeld	Naarheid, diarree, braking
	Minder gereeld	Abdominale pyn, boonste abdominale pyn, droë mond, dispepsie, ongemak in die maag, abdominale distensie, askites, hardlywigheid, disfagie, flatulensie
Hepatobiliêre versteurings	Gereeld	Verhoogde lewerwaardes (alanien aminotransferase, aspartaat aminotransferase, alkaliese fosfatase in die bloed, gekonjugeerde bilirubien, bloedbilirubien)
	Minder gereeld	Cholestase, hepatomegalie, hiperbilirubinemie, geelsug, abnormale lewerfunksie, hepatotoksisiteit, lewerversteuring, verhoogde gamma-glutamieltransferase
Vel en subkutaneuse weefsel versteurings	Gereeld	Veluitslag, pruritus, eriteem, hiperhidrose
	Minder gereeld	Multiforme eriteem, makulêre uitslag, makulopapulêre uitslag, pruritiese uitslag, urtikarie, allergiese dermatitis, algemene pruritus, eritemateuse uitslag, algemene uitslag, morbillivormige uitslag, velletsel
	Frekwensie onbekend	Toksiese epidermale nekrolise, Stevens-Johnson-sindroom
Muskuloskeletale, bindweefsel- en beenversteurings	Gereeld	Artralgie
	Minder gereeld	Rugpyn, pyn in die ledemate, beenpyn, spierswakheid, mialgie
Renale- en urinêre versteurings	Minder gereeld	Nierversaking, akute nierversaking
Algemene versteurings en toedieningsplek toestande	Gereeld	Pireksie, koue rillings, pruritus by die infusieplek
	Minder gereeld	Pyn, pyn by die kateterplek, moegheid, koue gevoel, warm gevoel, eriteem by die infusieplek , infusieplek verharding, pyn by die infusieplek, swelling by die infusieplek, flebitis by die inspuitplek, perifere edeem, teerheid, borskas ongemak, borspyn, gesigs edeem, gevoel van liggaamstemperatuur verandering, verharding, ekstravasering by die infusieplek, irritasie by die infusieplek, flebitis op die infusieplek, uitslag by die infusieplek, infusieplek urtikarie, eriteem by die inspuitplek, edeem by die inspuitplek, pyn op die inspuitplek, swelling van die inspuitplek, malaise, edeem
Ondersoeke	Gereeld	Verhoogde lewertoetswaardes (aspartaat transaminase (AST)), alanientransaminase (ALT), alkaliese fosfatase, direkte en totale bilirubien) verminderde hemoglobien, verminderde hematokrit, lae kalium, lae albumien, verminderde witbloedselle
	Minder gereeld	Verhoogde bloedkreatinien, urien positiewe rooibloedselle, verminderde totale proteïen, proteïenurien teenwoordig, verlengde protrombientyd, verkorte protrombientyd, verminderde bloednatrium vlak, verhoogde bloednatrium vlak, verminderde kalsium in die bloed, verhoogde kalsium in die bloed, verlaagde bloedchloried, verhoogde bloedglukose, verminderde bloedmagnesium, verlaagde bloedfosfor, verhoogde bloedfosfor, verhoogde bloedureum, verlengde geaktiveerde gedeeltelike tromboplastientyd, verlaagde bloedbikarbonaat, verhoogde bloedchloried, verhoogde bloedkalium, verhoogde bloeddruk, verminderde uriensuur in die bloed, bloed urien teenwoordig, abnormale asemgeluide, verlaagde koolstofdioksied, verhoogde immuunonderdrukkende medisynevlak, verhoogde internasionale genormaliseerde verhouding, urinêre stortings, urien positiewe witbloedselle, en verhoogde urien pH

Pediatriese pasiënte
Die mees gereelde ongunstige ervarings wat aangemeld is in pediatriese pasiënte wat met CASFIN behandel is, was koors, veluitslag en hoofpyn.

MedDRA Sisteem Orgaan Klas	Frekwensie	Newe effekte
Bloed- en limfstelselversteurings	Gereeld	Verhoogde eosinofieltelling
Senuweestelsel versteurings	Gereeld	Hoofpyn
Kardiale versteurings	Gereeld	Tagikardie
Vaskulêre versteurings	Gereeld	Blosing, hipotensie
Hepatobiliêre versteurings	Gereeld	Verhoogde lewerensiemvlakke (AST, ALT)
Vel en subkutaneuse weefsel versteurings	Gereeld	Veluitslag, pruritus
Algemene versteurings en toedieningsplek toestande	Gereeld	Koors, koue rillings, pyn by die kateterplek
Ondersoeke	Gereeld	Verhoogde lewerensiemvlakke (AST, ALT) verlaagde kalium, hipomagnesemie, verhoogde glukose, verminderde fosfor, en verhoogde fosfor, verhoogde eosinofiele.

Aanmelding van vermoedelike ongewenste reaksies
Aanmelding van vermoedelike ongewenste reaksies na goedkeuring van die medisyne is belangrik. Dit laat volgehoue monitering van die voordeel/risiko balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike ongewenste reaksies by SAHPRA aan te meld via die **"6.04 Adverse Drug Reactions Reporting Form"**, wat aanlyn gevind kan word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
'n Dosis van 210 mg, toegedien as 'n enkel dosering aan gesonde volwasse proefpersone, is oor die algemeen goed verdra. Daarby is 'n dosering van 150 mg, toegedien aan volwasse pasiënte, een keer per dag vir tot 51 dae, oor die algemeen goed verdra.
Onopsetlike toediening van tot 400 mg van kaspofungien op een dag is aangemeld. Hierdie gebeure het nie klinies belangrike ongewenste reaksies tot gevolg gehad nie. Kaspofungien is nie dialiseerbaar nie.

5 FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
Farmakoterapeutiese groep: antimikotikum vir sistemiese gebruik ATC-kode: J02AX04. A 20.2.2 Antimikrobiese (chemoterapeutiese) middels: Fungisiede.

Werkingsmeganisme
Kaspofungien asetaat inhibeer die sintese van beta (1,3) -D-glukaan, 'n noodsaaklike komponent van die selwand van baie filamentagtige fungi en gis. Beta (1,3) -D-glukaan is nie teenwoordig in soogdierselle nie.

Kruisweerstandigheid
Kaspofungien asetaat is aktief teen *Candida* soorte met 'n intrinsieke of verworwe weerstand teen flukonasool, amfoterisien B of flusitosien, wat ooreenstem met hul verskillende werkingsmeganismes.

Weerstandsmeganisme
Mutante van *Candida* met 'n verminderde vatbaarheid vir kaspofungien is in sommige pasiënte tydens behandeling geïdentifiseer. MIK (minimum-inhiberende-konsentrasie) waardes vir kaspofungien moet nie gebruik word om kliniese uitkoms te voorspel nie, aangesien 'n korrelasie tussen MIK waardes en kliniese uitkoms nie vasgestel is nie.

5.2 Farmakokinetiese eienskappe
Verspreiding
Plasmakonsentrasies van kaspofungien neem af in 'n polifasiese manier na enkel 1-uur intraveneuse infusies. 'n Kort alfa-fase vind onmiddellik na infusie plaas, gevolg deur 'n beta-fase met 'n halfleeftyd van 9 tot 11 ure, wat kenmerkend is vir 'n groot deel van die profiel en 'n duidelike loglineêre gedrag toon, vanaf 6 tot 48 ure na dosering, waartydens die plasmakonsentrasie 10-voudig afneem. 'n Bykomende gamma-fase vind ook plaas (halfleeftyd 40 tot 50 ure). Verspreiding, eerder as uitskeiding of biotransformasie, is die dominante meganisme wat plasma-opruiming beïnvloed.
Kaspofungien is omvattend gebind aan albumien (ongeveer 97 %), en verspreiding in rooibloedselle is minimaal. Massabalans resultate het getoon dat ongeveer 92 % van die toegediende radioaktiwiteit, teen 36 tot 48 uur na 'n enkel 70 mg dosis [³H] kaspofungien asetaat, na weefsel versprei het. Daar is min uitskeiding of biotransformasie van kaspofungien gedurende die eerste 30 uur na toediening.

Biotransformasie
Kaspofungien word stadig gemetaboliseer deur hidrolise en N-asetilering, en ondergaan spontane chemiese afbraak na 'n oopring-peptiedverbinding.
Na enkeldosis toediening van [³H] kaspofungien asetaat, is daar op latere tydpunte 'n lae vlak van kovalente binding van radio-merk in plasma, wat moontlik kan wees as gevolg van twee reaktiewe tussenstowwe wat gevorm word tydens die chemiese afbraak van kaspofungien. Addisionele metabolisme behels hidrolise in samestellende aminosure en hul derivate, insluitend dihidroksiehomotirosien en *N*-asetiel-dihidroksiehomotirosien. Hierdie twee tirosienderivate word slegs in uriene aangetref, wat dui op vinnige opruiming van hierdie derivate deur die niere.

Eliminasie
In enkeldosis radio-gemerkte farmakokinetiese studies is plasma, uriene en feses oor 27 dae versamel, of plasma is oor 6 maande versamel. Ongeveer 75 % van die radioaktiwiteit is herwin: 41 % in uriene en 34 % in feses. Plasmakonsentrasies van radioaktiwiteit en van kaspofungien was soortgelyk gedurende die eerste 24 tot 48 uur na dosering; daarna het die medisynevlakke vinniger gedaal. In plasma het die kaspofungienkonsentrasies, na 6 tot 8 dae na dosering, geval tot onder die kwantifiseringslimiet, terwyl radio-merk teen 22,3 weke na die dosering, tot onder die kwantifiseringslimiet geval het. Renale opruiming van moederstof is laag (ongeveer 0,15 ml/min).
'n Klein hoeveelheid van kaspofungien word onveranderd in die uriene uitgeskei (ongeveer 1,4 % van die dosis).

Lineariteit/nie-lineariteit
Kaspofungien vertoon matige nie-lineêre farmakokinetika met verhoogde akkumulasie namate die dosis verhoog word, en 'n dosisafhanklikheid in die tyd om 'n gelykvlak te bereik op meervoudige toediening.

Spesiale populasies
Gewig: Daar is gevind dat gewig die farmakokinetieka van kaspofungien, in die populasie farmakokinetiese analise in volwasse kandidiase pasiënte beïnvloed. Die plasmakonsentrasies neem af met toenemende gewig. Daar is voorspel dat die gemiddelde blootstelling ongeveer 23 % laer sou wees in 'n volwasse pasiënt wat 80 kg weeg, as in 'n volwasse pasiënt wat 60 kg weeg.
Hepatiese inkorting: In volwasse pasiënte met ligte en matige hepatiese inkorting, word die AOK onderskeidelik met 20 en 75 % verhoog. Daar is geen kliniese ondervinding in volwasse pasiënte met ernstige hepatiese inkorting, en in pediatriese pasiënte met enige mate van hepatiese inkorting nie. In 'n meervoudige dosis studie is getoon dat 'n dosisverlaging van die daaglikse dosis tot 35 mg in volwasse pasiënte met matige hepatiese inkorting, 'n AOK bied wat soortgelyk is aan die wat verkry is in volwasse proefpersone met normale hepatiese funksie wat die standaardregime ontvang (sien afdeling 4.2).
Renale inkorting: In 'n kliniese studie van enkel 70 mg doserings, was die farmakokinetieka van kaspofungien soortgelyk in volwasse vrywilligers met ligte renale inkorting (kreatinienopruiming 50 tot 80 ml/min) en kontrole proefpersone. Matige- (kreatinienopruiming 31 tot 49 ml/min), gevorderde- (kreatinienopruiming 5 tot 30 ml/min) en eindstadium nierversaking (kreatinienopruiming <10 ml/min en dialise afhanklik) het kaspofungien plasma konsentrasies matig verhoog, na enkeldosis toediening (reeks: 30 tot 49 % vir AOK). In volwasse pasiënte met indringende kandidiase, esofagus kandidiasis of indringende aspergillose wat veelvuldige daaglikse 50 mg kaspofungien doserings ontvang het, was daar egter geen beduidende effek van ligte tot gevorderde nierinkorting op kaspofungien konsentrasies nie. Geen dosisaanpassing is nodig vir pasiënte met renale inkorting nie. Kaspofungien is nie dialiseerbaar nie, dus is aanvullende dosering nie nodig na hemodialise nie.
Geslag: Kaspofungien plasmakonsentrasies was gemiddeld 17 tot 38 % hoër in vrouens as in mans.
Bejaardes: 'n Beskeie toename in AOK (28 %) en K_{24h} (32 %) is in ouer manlike proefpersone waargeneem in vergelyking met jong manlike proefpersone. In pasiënte wat empiries behandel is of wat indringende kandidiase gehad het, was 'n soortgelyke beskeie effek van ouderdom in ouer pasiënte waargeneem in vergelyking met jonger pasiënte.

Pediatriese populasie
In adolessente (tussen 12 en 17 jaar) wat kaspofungien 50 mg/m² (maksimum 70 mg daagliks) daagliks ontvang, is die kaspofungienplasma $AOK_{0\text{-}24uur}$ oor die algemeen vergelykbaar met die wat in volwassenes wat 50 mg kaspofungien daagliks ontvang.
In kinders (ouderdomme 2 tot 11 jaar) wat kaspofungien 50 mg/m² (maksimum 70 mg daagliks) daagliks ontvang, is die kaspofungien plasma $AOK_{0\text{-}24uur}$ na meervoudige dosisse vergelykbaar met die wat gesien word by volwassenes wat kaspofungien 50 mg/dag ontvang.
In jong kinders en kleuters (ouderdomme 12 tot 23 maande) wat kaspofungien 50 mg/m² (maksimum 70 mg daagliks) daagliks ontvang, is die kaspofungien plasma $AOK_{0\text{-}24uur}$ na meervoudige dosisse vergelykbaar met die wat gesien word in volwassenes wat 50 mg kaspofungien daagliks ontvang en by ouer kinders (2 tot 11 jaar) wat die daaglikse dosis van 50 mg/m² ontvang**.**
Oor die algemeen is die beskikbare farmakokinetiese-, effektiwiteits- en veiligheidsdata beperk in pasiënte van 3 tot 10 maande oud.
In pasgeborenes en babas (< 3 maande) wat kaspofungien teen 25 mg/m² (ooreenstemmende gemiddelde daaglikse dosis van 2,1 mg/kg) daagliks ontvang, word die kaspofungien piekkonsentrasie (K_{1uur}) en kaspofungien trog konsentrasie (K_{24uur}) na meervoudige dosisse vergelykbaar met die wat gesien word in volwassenes wat 50 mg kaspofungien daagliks ontvang. Die effektiwiteit en veiligheid van kaspofungien is nie voldoende bestudeer in voornemende kliniese proewe wat pasgeborenes en babas jonger as 3 maande oud betrek nie.

6 FARMASEUTIESE EIENSKAPPE
6.1 Lys van onaktiewe bestanddele
Sukrose, Mannitol (E421), Koolstofdioksied (E290) (pH-aanpassing), Soutsuur, konsentraat (E507) (pH-aanpassing), Natriumhidroksied (E524) (pH-aanpassing), Water vir inspuiting.

6.2 Onverenigbaarhede
Moet nie meng met verdunningsmiddels wat dekstrose bevat nie, aangesien CASFIN nie stabiel is in verdunningsmiddels wat dekstrose bevat nie. In die afwesigheid van verenigbaarheidstudies, moet CASFIN nie met ander medisyne gemeng word nie.

6.3 Rakleeftyd
36 maande (bewaar by 2 ºC tot 8 ºC).
Na hersamestelling kan CASFIN 50 en 70 mg poeier vir konsentraat vir oplossing vir infusie tot 24 uur by of benede 25 ºC bewaar word. Stabiliteitsdata het getoon dat CASFIN 50 en 70 mg poeier vir konsentraat vir oplossing vir infusie binne 24 uur gebruik kan word wanneer dit by 25 ºC of benede bewaar word, of binne 48 uur wanneer die intraveneuse infusiesak (bottel) in 'n yskas bewaar word (2 ° C tot 8 ºC) en verdun is met natriumchloriedoplossing 9 mg/ml (0,9 %), 4,5 mg/ml (0,45 %) of 2,25 mg/ml (0,225 %) vir infusie, of Ringerslaktaat oplossing. CASFIN bevat geen preserveermiddels nie. Vanuit 'n mikrobiologiese oogpunt moet CASFIN onmiddellik gebruik word. Indien nie onmiddellik gebruik word nie, is die in-gebruik bewaringstye en -voorwaardes voor gebruik die verantwoordelikheid van die gebruiker en is dit gewoonlik nie langer as 24 uur by 2 ° C tot 8 ° C nie, tensy hersamestelling en verdunning plaasgevind het onder gekontroleerde, gevalideerde aseptiese toestande .

6.4 Spesiale voorsorgmaatreëls vir bewaring
Onoopgemaakte flessies: Bewaar in 'n yskas (2 °C tot 8 °C). Vir bewaringstoestande na hersamestelling en verdunning van CASFIN, sien afdeling 6.3.

6.5 Aard en inhoud van houer
CASFIN 50: 10 ml glas flessie met 'n rubberprop en 'n aluminiumseël met 'n rooi plastiek afwip dop.
CASFIN 70: 10 ml glas flessie met 'n rubberprop en 'n aluminiumseël met 'n oranje plastiek afwip dop.
'n Enkel flessie is verpak in 'n buitenste karton.

6.6 Spesiale voorsorgmaatreëls vir vernietiging en ander hantering
Hersamestelling van CASFIN
MOET GEEN VERDUNNINGSMIDDELS WAT DEKTROSE BEVAT GEBRUIK NIE.
CASFIN is nie stabiel in verdunningsmiddels wat dekstrose bevat nie.
MOET NIE CASFIN MET ENIGE ANDER GENEESMIDDELS MENG, OF GELYKTYDIGE INFUSIE TOEDIEN NIE.
Daar is geen data beskikbaar oor die verenigbaarheid van CASFIN met ander intraveneuse stowwe, bymiddels of medisyne nie.
Inspekteer die infusie oplossing visueel vir sigbare deeltjies of verkleuring. Moet nie die oplossing gebruik indien die oplossing troebel is of neerslag gevorm het nie. CASFIN is geformuleer om die volle geëtiketeerde dosis per flessie (50 mg of 70 mg) te verskaf wanneer 10 ml uit die flessie onttrek word.

Instruksies vir gebruik in volwassenes
Stap 1: Hersamestelling van flessies
Vir hersaamstelling van die verpoeierde medisyne, bring die verkoelde CASFIN flessie tot kamertemperatuur en voeg asepties 10,5 ml Steriele Water vir Inspuiting by. Die konsentrasies van die hersaamgestelde flessies sal wees: 7,2 mg/ml (70 mg flessie) of 5,2 mg/ml (50 mg flessie).
Die wit tot naaswit kompakte poeier sal heeltemal oplos. Meng versigtig totdat 'n helder oplossing verkry word. Hersaamgestelde oplossings moet visueel ondersoek word vir sigbare deeltjies of verkleuring. Hierdie hersaamgestelde oplossing kan vir tot 24 uur by of benede 25 ° C bewaar word.

Stap 2: Byvoeging van Hersaamgestelde CASFIN by die infusieoplossing van die pasiënt
Verdunningsmiddels vir die finale pasiëntinfusie oplossings is: Steriele Soutoplossing vir Inspuiting of Ringerslaktaatoplossing. Die standaard pasiënt infusie word voorberei deur aseptiese byvoeging van die gepaste hoeveelheid hersaamgestelde CASFIN (soos getoon in die onderstaande tabel) tot 'n 250 ml intraveneuse sak of bottel. Infusies met verminderde volume in 100 ml kan, indien medies nodig, gebruik word vir daaglikse dosisse van 50 mg of 35 mg. Moet nie gebruik indien die oplossing troebel is of neerslag gevorm het nie. Hierdie infusie oplossing moet binne 24 uur gebruik word indien dit by of benede 25 ° C geberg word, of binne 48 uur indien dit in die yskas gestoor word by 2 tot 8 ° C. CASFIN moet toegedien word deur stadige intraveneuse infusie oor ongeveer 1 uur.

Voorbereiding van die infusie oplossings vir volwasse pasiënte

DOSIS*	Volume van hersaamgestelde CASFIN vir oordrag na intraveneuse sak of bottel	Standaard voorbereiding (hersaamgestelde CASFIN bygevoeg by 250 ml) finale konsentrasie	Verminderde volume infusie (hersaamgestelde CASFIN bygevoeg by 100 ml) finale konsentrasie
70 mg	10 ml	0,28 mg/ml	Nie aanbeveel nie
70 mg (van twee 50 mg flessies)**	14 ml	0,28 mg/ml	Nie aanbeveel nie
50 mg	10 ml	0,20 mg/ml	0,47 mg/ml
35 mg vir matige hepatiese inkorting (van een 70 mg flessie)	5 ml	0,14 mg/ml	0,34 mg/ml
35 mg vir matige hepatiese inkorting (van een 50 mg flessie)	7 ml	0,14 mg/ml	0,34 mg/ml

*10,5 ml moet gebruik word vir hersamestelling van alle flessies.
** Indien 'n 70 mg flessie nie beskikbaar is nie, kan die 70 mg dosering uit twee 50 mg flessies berei word.

Instruksies vir gebruik in pediatriese pasiënte
Berekening van Liggaamsoppervlakte area (LOA) vir pediatriese dosering
Bereken die liggaamsoppervlakte area (LOA) van die pasiënt voordat die infusie voorberei word deur die volgende formule (Mosteller Formule) te gebruik:

$$LOA\ (m^2) = \sqrt{\frac{\text{Lengte (cm) x Gewig (kg)}}{3600}}$$

Voorbereiding van die 70 mg/m² infusie vir pediatriese pasiënte > 3 maande oud (met gebruik van 'n 70 mg flessie)
1. Bepaal die werklike ladingsdosis wat in die pediatriese pasiënt gebruik moet word deur die LOA van die pasiënt (soos hierbo bereken) en die volgende vergelyking te gebruik:
   LOA (m²) X 70 mg/m² = Ladingsdosis
   Die maksimum ladingsdosis op Dag 1 moet nie 70 mg oorskry nie, ongeag die berekende dosis van die pasiënt.
2. Bring die verkoelde flessie van CASFIN in ewewig met kamertemperatuur.
3. Voeg 10,5 ml Steriele Water vir Inspuiting, asepties by. Hierdie hersaamgestelde oplossing kan vir tot 25 uur by 25 ° C bewaar word. Dit sal 'n finale kaspofungien konsentrasie van 7,2 mg/ml in die flessie gee.
4. Verwyder die volume van medisyne gelykstaande aan die berekende ladingsdosis (Stap 1) vanuit die flessie. Dra hierdie volume (ml) hersaamgestelde CASFIN asepties oor na 'n IV -sakkie (of -bottel) wat 250 ml van 0,9 %, 0,45 % of 0,225 % Natriumchloriedinspuiting of Ringerslaktaat Inspuiting bevat. Alternatiewelik kan die volume (ml) hersaamgestelde CASFIN bygevoeg word tot 'n verminderde volume van 0,9 %, 0,45 % of 0,225 % Natriumchloriedinspuiting of Ringerslaktaat Inspuiting, om nie die finale konsentrasie van 0,5 mg/ml te oorskry nie. Hierdie infusie oplossing moet binne 24 uur gebruik word indien dit by of benede 25 ° C geberg word of binne 48 uur indien dit in die yskas bewaar word by 2 tot 8 ° C.
5. Indien die berekende ladingsdosis minder as 50 mg is, kan die dosis voorberei word uit die 50 mg flessie [volg Stappe 2 tot 4 van die *Voorbereiding van die 50 mg/m² infusie vir pediatriese pasiënte > 3 maande oud (met gebruik van 'n 50 mg flessie)]*. Die finale kaspofungien konsentrasie in die 50 mg flessie na hersamestelling is 5,2 mg/ml.

Voorbereiding van die 50 mg/m² infusie vir pediatriese pasiënte > 3 maande oud (met gebruik van 'n 50 mg flessie)
1. Bepaal die daaglikse onderhoudsdosis wat in die pediatriese pasiënt gebruik moet word deur die LOA van die pasiënt (soos hierbo bereken) en die volgende vergelyking te gebruik:
   LOA (m²) X 50 mg/m² = Daaglikse Onderhoudsdosis
   Die daaglikse onderhoudsdosis moet nie 70 mg oorskry nie, ongeag die berekende dosis van die pasiënt.
2. Bring die verkoelde flessie van CASFIN in ewewig met kamertemperatuur.
3. Voeg 10,5 ml Steriele Water vir Inspuiting asepties by. Hierdie hersaamgestelde oplossing kan vir tot 24 uur by 25 ° C gestoor word. Dit gee 'n finale kaspofungien konsentrasie van 5,2 mg/ml, in die flessie.
4. Verwyder die volume CASFIN gelykstaande aan die berekende daaglikse onderhoudsdosis (Stap 1) uit die flessie.
5. Dra hierdie volume (ml) hersaamgestelde CASFIN asepties oor na 'n IV- sakkie (of - bottel) wat 250 ml 0,9 %, 0,45 %of 0,225 % Natriumchloriedinspuiting of Ringerslaktaat Inspuiting bevat. Alternatiewelik kan die volume (ml) hersaamgestelde CASFIN bygevoeg word tot 'n verminderde volume van 0,9 %, 0,45 % of 0,225 % Natriumchloriedinspuiting of Ringerslaktaat Inspuiting, om nie die finale konsentrasie van 0,5 mg/ml te oorskry nie. Hierdie infusie oplossing moet binne 24 uur gebruik word indien dit by 25 ° C of benede gestoor word, of binne 48 uur indien dit in die yskas gestoor word by 2 tot 8 ° C.
6. Indien die werklike daaglikse onderhoudsdosis > 50 mg is, kan die dosis voorberei word uit die 70 mg flessie [volg Stappe 2 tot 4 van die *Voorbereiding van die 70 mg/m² infusie vir pediatriese pasiënte > 3 maande of ouer (met gebruik van 'n 70 mg flessie)]*. Die finale kaspofungien konsentrasie in die 70 mg flessie, na hersamestelling is 7,2 mg/ml.

7 HOUER VAN REGISTRASIESERTIFIKAAT
Kahma Biotech (Edms) Bpk. 16de Weg, 106, Midrand

8 REGISTRASIENOMMERS
CASFIN 50: 55/20.2.2/0236
CASFIN 70: 55/20.2.2/0237

9 DATUM VAN EERSTE GOEDKEURING/HERNUWING VAN DIE GOEDKEURING
7 Junie 2022

10 DATUM VAN HERSIENING VAN DIE TEKS
N.A.

310 mm

Dimensions: 310 x 570 ± 2 mm
Font Style: Helvetica Neue LT Com
Font Size: 6 pt
Text matter print both sides on Bible Paper with 3 columns.