PROFESSIONAL INFORMATION

CASCAGIN 50

CASCAGIN 70

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CASCAGIN 50 (50 mg) lyophilised powder for solution for IV infusion.

CASCAGIN 70 (70 mg) lyophilised powder for solution for IV infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CASCAGIN 50:

Each 10 ml vial contains 50 mg caspofungin (as acetate).

The concentration of the reconstituted vials is 5,2 mg/ml.

Excipients with known effect:

Each vial contains 35,7 mg of sucrose.

CASCAGIN 70:

Each 10 ml vial contains 70 mg caspofungin (as acetate).

The concentration of the reconstituted vials is 7,2 mg/ml.

Excipients with known effect:

Each vial contains 50,0 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for solution for IV infusion.

Before reconstitution, it is a lyophilised white to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CASCAGIN is indicated in adults for:

- Empirical treatment for presumed fungal infections in febrile, neutropenic patients.
- Treatment of invasive candidiasis, including candidaemia.
- Treatment of oesophageal or oropharyngeal candidiasis where IV antifungal treatment 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 caspofungin in paediatric patients aged 3 months to 17 years are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in paediatric patients, and additional data from prospective studies in paediatric patients 3 months to 17 years of age.

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

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

4.2 Posology and method of administration

Posology

Empirical treatment (adult patients)

A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter.

If the 50 mg is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. Although an increase in efficacy with 70 mg daily has not been demonstrated, safety data suggest that an increase in dose to 70 mg daily is well tolerated.

Duration of treatment should be based on the patient's clinical response. Empirical treatment should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms have resolved.

Invasive Candidiasis (adult patients)

A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter.

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. Caspofungin is generally well tolerated in these patients receiving higher doses; however, the efficacy at this higher dose are generally similar to patients receiving a 50 mg daily dose.

Duration of treatment of invasive candidiasis 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 treatment duration pending resolution of the neutropenia.

Oesophageal and Oropharyngeal Candidiasis (adult patients)

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.

The efficacy of a 70 mg dose regimen in patients who are not clinically responding to the 50 mg daily dose is unknown. 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.

Duration of treatment should be determined on a case by case basis and be based upon the severity of the patient's underlying disease, recovery from immunosuppression and clinical response.

Special populations

Elderly patients

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

Hepatic impairment

Adult patients with mild hepatic insufficiency (Child-Pugh score: 5 - 6) do not require a dosage adjustment. For adult patients with moderate hepatic insufficiency (Child-Pugh score: 7 - 9), CASCAGIN 35 mg daily is recommended based on pharmacokinetic data. However, a 70 mg loading dose should still be administered on Day 1, where recommended. There is no clinical experience in adult patients with severe hepatic insufficiency (Child-Pugh score: > 9) and in paediatric patients with any degree of hepatic insufficiency (see section 4.3).

Co-administration with inducers of metabolic enzymes

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

Renal impairment

No dosage adjustment is necessary based on renal impairment (see section 5.2).

Race / Gender

No dosage adjustment is necessary based on gender or race (see section 5.2).

Paediatric population

Dosing in children and adolescents should be based on the patient's body surface area (see "Instructions for Use in Paediatric Patients, Mosteller [A]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).

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.

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

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:

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

Duration of treatment should be individualised to the indication, as described for each indication in adults, above.

When caspofungin is co-administered to paediatric patients with inducers of metabolic enzymes (see section 4.5), a caspofungin dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

Method of administration

Caspofungin should be given as a single daily infusion.

After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour. For reconstitution directions see section 6.6.

Both 70 mg and 50 mg vials are available.

4.3 Contraindications

CASCAGIN is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

CASCAGIN has not been studied in severe hepatic insufficiency or in paediatric patients with any degree of hepatic impairment.

4.4 Special warnings and precautions for use

Anaphylaxis has been reported during administration of caspofungin. If this occurs, CASCAGIN should be discontinued and appropriate treatment administered. Possible histamine-mediated symptoms including reports of rash, facial swelling, angioedema, pruritus, sensation of warmth or bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment.

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

Concomitant use of caspofungin with ciclosporin has been evaluated in adult healthy volunteers and in adult patients. Some healthy adult subjects who received two 3 mg/kg doses of ciclosporin with caspofungin showed transient increases in ALT and AST of ≤ 3-fold the upper limit of normal (ULN) that resolved upon discontinuation of these medicines. There was also an increase of approximately 35 % in the area under the curve (AUC) of caspofungin when co-administered with ciclosporin; however, blood levels of ciclosporin remained unchanged. Close monitoring of liver enzymes should be considered if the two medicines are used concomitantly (see section 4.5).

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

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

CASCAGIN contains sucrose. Patients with rare hereditary problems of fructose intolerance or sucrase-isomaltase insufficiency should not be given CASCAGIN (see section 2).

4.5 Interaction with other medicines and other forms of interaction

Studies *in vitro* show that caspofungin acetate is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. In clinical studies, caspofungin did not induce the CYP3A4

metabolism of other medicines. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes. However, caspofungin has been shown to interact with other medicines in pharmacological and clinical studies (see below).

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.

In two adult clinical studies, ciclosporin (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35 %. These AUC increases are probably due to reduced uptake of caspofungin by liver. Caspofungin did not increase the plasma levels of ciclosporin. There were transient increases in liver ALT and AST when caspofungin and ciclosporin were co-administered. A retrospective study of 40 patients treated during marketed use of caspofungin and/or ciclosporin for 1 to 290 days (median 17,5 days), indicated no serious hepatic adverse events (see section 4.4). Close monitoring of liver enzymes should be considered if the two medicines are used concomitantly.

Clinical studies indicate that the pharmacokinetics of caspofungin are not altered by itraconazole, amphotericin B, mycophenolate, nelfinavir or tacrolimus. Caspofungin has no effect on the pharmacokinetics of itraconazole, amphotericin B, rifampicin or the active metabolite of mycophenolate. Although safety data is limited it appears that no special precautions are needed when these medicines are co-administered with caspofungin.

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

Results from clinical interaction studies in healthy adult volunteers 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 caspofungin may also result in clinically meaningful reductions in caspofungin concentrations. Available data suggest that the inducible medicine clearance mechanism involved in caspofungin disposition is likely an uptake transport process, rather than metabolism. Therefore, when CASCAGIN 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, following the 70 mg loading dose, should be considered (see section 4.2).

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

Paediatric population

In paediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with caspofungin may result in clinically meaningful reductions in caspofungin trough concentrations. This finding may indicate that paediatric patients will have similar reductions with inducers as seen in adults. When CASCAGIN is co-administered to paediatric patients with inducers of medicine clearance (for example rifampin, efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine) a dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

CASCAGIN should not be used during pregnancy as there is no clinical experience involving

pregnant women. Animal studies have shown developmental toxicity and caspofungin has been shown to cross the placental barrier in animal studies.

Breastfeeding

It is not known whether CASCAGIN is excreted in human milk; therefore, women receiving CASCAGIN should not breastfeed.

Fertility

Studies conducted in male and female rats do not indicate any effects on fertility. There is no clinical data for caspofungin to assess its impact on fertility.

4.7 Effects on ability to drive and use machines

There is no data available on whether CASCAGIN impairs the ability to drive or operate machinery. However, CASCAGIN can cause dizziness, disorientation, blurred vision and somnolence (see section 4.8). Patients should be warned not to drive or operate machinery until they are aware of the measure to which CASCAGIN affects them or until such side effects subside.

4.8 Undesirable effects

Summary of the safety profile

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

In patients with invasive aspergillosis, pulmonary oedema, adult respiratory distress syndrome (ARDS) and radiographic infiltrates have been reported.

Phlebitis is a common local injection-site adverse reaction. Other local reactions include erythema, pain/tenderness, itching, discharge and a burning sensation.

Reported clinical and laboratory abnormalities were typically mild and rarely led to discontinuation.

A study compared caspofungin at 50 mg daily (following a 70 mg loading dose on Day 1) versus 150 mg daily in the treatment of invasive candidiasis. In this group of patients, the safety of caspofungin at this higher dose appeared generally similar to patients receiving the 50 mg daily caspofungin dose. The proportion of patients with a serious drug-related adverse reaction or a drug-related adverse reaction leading to caspofungin discontinuation was comparable in both treatment groups.

Tabulated list of adverse reactions

Blood and lymphatic system disorders:

Frequent: Anaemia, haemoglobin decreased, haematocrit decreased and white blood cell count decreased.

Less frequent: Thrombocytopenia, coagulopathy, leukopenia, eosinophil count increased, platelet count decreased, platelet count increased, lymphocyte count decreased, white blood cell count increased and neutrophil count decreased.

Metabolism and nutrition disorders:

Frequent: Hypokalaemia.

Less frequent: Fluid overload, hypomagnesaemia, anorexia, electrolyte imbalance, hyperglycaemia, hypocalcaemia and metabolic acidosis.

Psychiatric disorders:

Less frequent: Anxiety, disorientation and insomnia.

Nervous system disorders:

Frequent: Headache.

Less frequent: Dizziness, dysgeusia, paraesthesia, somnolence, tremor and hypoaesthesia.

Eye disorders:

Less frequent: Ocular icterus, vision blurred, eyelid oedema and lacrimation increased.

Cardiac disorders:

Less frequent: Palpitations, tachycardia, dysrhythmia, atrial fibrillation and cardiac failure congestive.

Vascular disorders:

Frequent: Phlebitis/thrombophlebitis.

Less frequent: Flushing, hot flush, hypertension and hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea.

Less frequent: Nasal congestion, pharyngolaryngeal pain, tachypnoea, bronchospasm, cough, dyspnea paroxysmal nocturnal, hypoxia, rales and wheezing.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea and vomiting.

Less frequent: Abdominal pain, upper abdominal pain, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia and flatulence.

Hepatobiliary disorders:

Frequent: Elevated liver values (alanine aminotransferase, aspartate aminotranserase, blood alkaline phosphatase, bilirubin conjugated, and blood bilirubin).

Less frequent: Cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, hepatotoxicity, liver disorder, hepatic function abnormal and gamma-glutamyltransferase increased.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus, sweating and erythema.

Less frequent: Erythema multiforme, rash macular, rash maculopapular, rash pruritic, urticaria, dermatitis allergic, pruritus generalised, rash erythematous, rash generalised, rash morbilliform and 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 and myalgia.

Renal and urinary disorders:

Less frequent: Renal failure and renal failure acute.

General disorders and administration site conditions:

Frequent: Fever, chills and 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, 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, oedema peripheral and swelling.

Investigations:

Frequent: Blood potassium decreased and blood albumin decreased.

Less frequent: Blood creatinine increased, red blood cells urine positive, protein total decreased, protein urine present, prothrombin time prolonged, prothrombin time shortened, blood sodium decreased, blood sodium increased, blood chloride decreased, blood glucose increased, blood magnesium decreased, blood phosphorus decreased, blood phosphorus increased, blood urea increased, activated partial thromboplastin time prolonged, blood bicarbonate decreased, blood chloride increased, blood potassium increased, blood pressure increased, blood uric acid decreased, blood urine present, breath sounds abnormal, carbon dioxide decreased, immunosuppressant drug level increased, international normalised ratio increased, urinary casts, white blood cells urine positive, pH urine increased, blood calcium decreased and blood calcium increased.

Paediatric population

The overall clinical safety profile of caspofungin in paediatric patients is comparable to that in adult patients. Reported drug-related clinical and laboratory abnormalities among all paediatric patients treated with caspofungin are typically mild and rarely led to discontinuation. The most common drug-related clinical adverse experiences reported in paediatric patients treated with

caspofungin were pyrexia, rash and headache.

Blood and lymphatic system disorders:

Frequent: Eosinophil count increased.

Nervous system disorders:

Frequent: Headache.

Cardiac disorders:

Frequent: Tachycardia.

Vascular disorders:

Frequent: Flushing and hypotension.

Skin and subcutaneous tissue disorders:

Frequent: Rash and pruritus.

General disorders and administration site conditions:

Frequent: Fever, chills and catheter site pain.

Investigations:

Frequent: Elevated liver enzyme levels (AST, ALT), decreased potassium, hypomagnesaemia, increased glucose, decreased phosphorus and increased phosphorus.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "*6.04*

Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

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

Pharmacological Classification: A.20.2.2. Antimicrobial (Chemotherapeutic Agents): Fungicides.

Pharmacotherapeutic group: antimycotics for systemic use.

ATC Code: J02AX04.

Mechanism of action

Caspofungin acetate is a semi-synthetic lipopeptide (echinocandin) compound.

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.

Fungicidal activity with caspofungin has been demonstrated against *Candida* yeasts. Studies *in vitro* and *in vivo* demonstrate that exposure of *Aspergillus* to caspofungin results in lysis and death of hyphal apical tips and branch points where cell growth and division occur.

Pharmacodynamic effects

Caspofungin has *in vitro* activity against *Aspergillus* species (including *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus* and *Aspergillus candidus*) and *Candida* species (including *Candida albicans, Candida dubliniensis, Candida glabrata, Candida guilliermondii, Candida kefyr, Candida krusei, Candida lipolytica, Candida lusitaniae, Candida parapsilosis, Candida rugosa* and *Candida tropicalis*), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B and 5-flucytosine. Susceptibility testing was performed according to a modification of both the Clinical and Laboratory Standards Institute (CLSI) formerly known as the National Committee for Clinical Laboratory Standards [NCCLS] method M38-A2 (for *Aspergillus* species) and method M27-A3 (for *Candida* species).

Standardised techniques for susceptibility testing have been established for yeasts by EUCAST. EUCAST breakpoints have not yet been established for caspofungin due to significant inter-laboratory variation in MIC ranges for caspofungin. *In lieu* of breakpoints, *Candida* isolates that are susceptible to anidulafungin and micafungin should be considered susceptible to caspofungin. Similarly, *C. parapsilosis* isolates intermediate to anidulafungin and micafungin can be regarded intermediate to caspofungin.

Resistance

Mutants of Candida with reduced susceptibility to caspofungin have been identified in some patients during treatment. A caspofungin MIC of ≤ 2 µg/ml using the CSLI M27-A3 method indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations > 2 µg/ml for growth inhibition have developed in a mouse model of *C. albicans* infection and in some patients with *Candida* infections. The mechanism of resistance identified is FKS1 and/or FKS2 (for *C. glabrata*) gene mutations. These cases have been associated with poor clinical outcomes.

Development of *in vitro* resistance to caspofungin by *Aspergillus* species has been identified. In limited clinical experience, resistance in patients with invasive aspergillosis has been observed. The incidence of resistance to caspofungin by various clinical isolates of *Aspergillus* is rare and resistance in *Candida* has been observed but the incidence may differ by species or region.

Cross-resistance

Caspofungin acetate is active against strains of *Candida* with intrinsic or acquired resistance to fluconazole, amphotericin B or flucytosine consistent with their different mechanisms of action.

5.2 Pharmacokinetic properties

Distribution

Caspofungin plasma concentrations decline in a polyphasic manner following single 1-hour intravenous infusions. A short alpha-phase occurs immediately post-infusion, followed by a beta-phase with a half-life of 9 - 11 hours that characterises much of the profile and exhibits clear log-linear behaviour from 6 - 48 hours post-dose during which the plasma concentration decreases by 10-fold. An additional gamma-phase also occurs (half-life: 40 - 50 hours).

Distribution, rather than excretion or biotransformation, is the dominant mechanism that influences plasma clearance, and is the rate-controlling step in both the alpha- and beta-disposition phases.

Caspofungin is extensively bound to albumin (approximately 97 %) and distribution into red blood cells is minimal. The unbound fraction of caspofungin in plasma varies from 3,5 % in healthy volunteers to 7,6 % in patients with invasive candidiasis.

The distribution into tissues peaked at 1,5 to 2 days after dosing when 92 % of the dose was distributed into tissues. It is likely that only a small fraction of the caspofungin taken up into tissues later returns to plasma as parent compound. Therefore, elimination occurs in the

absence of a distribution equilibrium, and a true estimate of the volume of distribution is currently impossible to obtain.

Metabolism

Caspofungin is slowly metabolised by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open-ring peptide compound. Two intermediate products, formed during the degradation of caspofungin to this open ring compound, form covalent adducts to plasma proteins resulting in a low-level, irreversible binding to plasma proteins.

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, which suggests rapid clearance of these derivatives by the kidneys.

In vitro studies indicate that caspofungin is not an inhibitor of cytochrome P450 enzymes 1A2, 2A6, 2C9, 2C19, 2D6 or 3A4. Results from clinical studies show that caspofungin does not induce or inhibit the CYP3A4 metabolism of other medicines. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

Elimination

The elimination of caspofungin from plasma is slow with a clearance of 10 – 12 ml/min.

Approximately 75 % of the radioactivity was recovered during radio-labelled pharmacokinetic studies: 41 % in urine and 34 % in faeces. Plasma concentrations of radioactivity and of caspofungin were similar during the first 24 - 48 hours post-dose; thereafter medicine levels fell more rapidly. In plasma, caspofungin concentrations 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. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration. A small amount of caspofungin is excreted unchanged in urine (approximately 1,4 % of dose). Renal clearance of parent substance is low (approximately 0,15 ml/min).

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.

Characteristics in Patients

Increased caspofungin exposure was seen in adult patients with renal impairment and mild liver impairment, in female subjects, as well as in the elderly. Generally, the increase was modest and not large enough to warrant a dosage adjustment. In adult patients with moderate liver impairment or in higher weight patients, a dosage adjustment may be required (see below).

Weight

Weight has been found to influence caspofungin pharmacokinetics in the population pharmacokinetic analysis in adult candidiasis patients: 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 Insufficiency

Plasma concentrations of caspofungin after a single 70 mg dose in adult patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) were increased by approximately 55 % in area under the curve (AUC) compared to healthy control subjects. In a 14-day multiple-dose study (70 mg on Day 1 followed by 50 mg daily thereafter), plasma concentrations in adult patients with mild hepatic insufficiency were increased modestly (19 to 25 % in AUC) on Days 7 and 14 relative to healthy control subjects. In a multiple-dose study, a dose reduction of the daily dose to 35 mg in moderate hepatic impairment has been shown to provide an AUC similar to that obtained in subjects with normal hepatic function receiving the standard regime (see section 4.2). Caspofungin has not been studied in severe hepatic insufficiency and in paediatric patients with any degree of hepatic impairment.

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 - 80 ml/min) and control subjects. Moderate (creatinine clearance: 31 - 49 ml/min), advanced (creatinine clearance: 5 - 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. As caspofungin is not dialysable, supplementary dosing is not required following haemodialysis.

Gender

Caspofungin plasma concentrations were on average 17 - 38 % higher in women compared to men.

Elderly

The plasma concentration of caspofungin in healthy older men and women (65 years of age or more) was increased (approximately 28 % in AUC) compared to young healthy males. In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients. However, no dosage adjustment is necessary for elderly patients (65 years of age or more).

Race

Patient pharmacokinetic data indicate no clinically significant differences in the pharmacokinetic profile of caspofungin between different races.

Paediatric Patients

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

In adolescents, aged 12 to 17 years, receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses > 50 mg daily, and some received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.

In children, aged 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 was comparable to that seen in adults receiving caspofungin at 50 mg/day. On the first day of administration, $AUC_{0\text{-}24hr}$ was somewhat higher in children than adults for these comparisons (37 % increase for the 50 mg/m^2/day to 50 mg/day comparison). However, the AUC values in these children on Day 1 were still less than those seen in adults at steady-state conditions.

In young children and toddlers, aged 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 was 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. Pharmacokinetic data from one 10-month old child receiving the 50 mg/m^2 daily dose indicated an $AUC_{0\text{-}24hr}$ within the same range as that observed in older children and adults at the 50 mg/m^2 and the 50 mg dose, respectively, while in one 6-month old child receiving the 50 mg/m^2 dose, the $AUC_{0\text{-}24hr}$ was somewhat higher.

Efficacy and safety 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

Carbon dioxide (to adjust the pH)

Hydrochloric acid (to adjust the pH)

Mannitol

Sodium hydroxide (to adjust the pH)

Sucrose

6.2 Incompatibilities

Do not mix with diluents containing glucose, as CASCAGIN is not stable in diluents containing glucose. In the absence of compatibility studies, CASCAGIN must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 2 years.

Reconstituted concentrate:

Use immediately. Stability data have shown that the concentrate for solution for infusion can be stored for up to 24 hours when the vial is stored at 25 °C or less and reconstituted with water for injection.

Diluted infusion solution:

Use immediately. Stability data have shown that CASCAGIN 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 at refrigerated conditions (2 – 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.

CASCAGIN does not contain any preservatives. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2 – 8 °C, unless reconstitution and dilution have taken place in controlled validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials: store in a refrigerator (2 °C – 8 °C).

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

6.5 Nature and contents of container

CASCAGIN 50 lyophilised powder is packed in a 10 ml Type I glass vial with a grey bromobutyl stopper and an aluminium flip-off seal with a top white plastic flip-off cap.

CASCAGIN 70 lyophilised powder is packed in a 10 ml Type I glass vial with a grey bromobutyl stopper and an aluminium flip-off seal with a top blue plastic flip-off cap.

Supplied in packs of 1 vial.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Reconstitution of CASCAGIN

Reconstituted CASCAGIN is a clear and colourless solution without any particulate matter.

DO NOT USE ANY DILUENTS CONTAINING GLUCOSE, as CASCAGIN is not stable in diluents containing glucose. **DO NOT MIX OR CO-INFUSE CASCAGIN WITH ANY OTHER MEDICINES**, as there is no data available on the compatibility of CASCAGIN with other intravenous substances, additives or medicines. Refer to section 6.3 for information on chemical-physical in-use shelf life after reconstitution and dilution.

VISUALLY INSPECT THE INFUSION SOLUTION FOR PARTICULATE MATTER OR DISCOLOURATION PRIOR TO USE.

For single use only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

CASCAGIN 50

INSTRUCTIONS FOR USE IN ADULT PATIENTS (CASCAGIN 50)

Step 1: Reconstitution of vials

To reconstitute the powder, bring the vial to room temperature and aseptically add 10,5 ml water for injection. The concentration of the reconstituted vials will be 5,2 mg/ml.

The white to off-white compact lyophilised 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 CASCAGIN 50 to infusion solution

Diluents for the final solution for infusion are: 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. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion 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.

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE*	**Volume of reconstituted CASCAGIN for transfer to intravenous bag or bottle**	**Standard preparation (reconstituted CASCAGIN added to 250 ml) final concentration**	**Reduced volume infusion (reconstituted CASCAGIN added to 100 ml) final concentration**
50 mg	10 ml	0,20 mg/ml	-

50 mg at reduced volume	10 ml	-	0,47 mg/ml
35 mg for moderate hepatic impairment (from one 50 mg vial)	7 ml	0,14 mg/ml	-
35 mg for moderate hepatic impairment (from one 50 mg vial) at reduced volume	7 ml	-	0,34 mg/ml

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

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS (CASCAGIN 50)

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

Preparation of the 70 mg/m^2 infusion for paediatric patients > 3 months of age (using a 50 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 to room temperature.
3. Aseptically add 10,5 ml of water for injection.
   a. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.
   b. This will give a final caspofungin concentration of 5,2 mg/ml per vial.
4. Remove the volume of CASCAGIN equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml) of reconstituted CASCAGIN 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 CASCAGIN 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 at refrigerated conditions (2 – 8 °C).

Preparation of the 50 mg/m^2 infusion for paediatric patients > 3 months of age (using a 50 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 50 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 to room temperature.
3. Aseptically add 10,5 ml of water for injection.
   a. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.
   b. This will give a final caspofungin concentration of 5,2 mg/ml per vial.
4. Remove the volume of CASCAGIN equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml) of reconstituted CASCAGIN 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 CASCAGIN 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 at refrigerated conditions (2 – 8 °C).

Preparation notes for CASCAGIN 50:

1. The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.
2. Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. DO NOT USE IF THE SOLUTION IS CLOUDY OR HAS PRECIPITATED.
3. CASCAGIN 50 is formulated to provide the full labeled vial dose (50 mg) when 10 ml is withdrawn from the vial.

CASCAGIN 70

INSTRUCTIONS FOR USE IN ADULT PATIENTS (CASCAGIN 70)

Step 1: Reconstitution of vials

To reconstitute the powder, bring the vial to room temperature and aseptically add 10,5 ml of water for injection. The concentration of the reconstituted vials will be 7,2 mg/ml.

The white to off-white compact lyophilised 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 CASCAGIN 70 to infusion solution

Diluents for the final solution for infusion are: 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. The solution for infusion is prepared by aseptically adding the appropriate amount of reconstituted concentrate (as shown in the table below) to a 250 ml infusion 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.

PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

DOSE*	**Volume of reconstituted CASCAGIN for transfer to intravenous bag or bottle**	**Standard preparation (reconstituted CASCAGIN added to 250 ml) final concentration**	**Reduced volume infusion (reconstituted CASCAGIN added to 100 ml) final concentration**
70 mg	10 ml	0,28 mg/ml	Not recommended
70 mg (from two 50 mg vial)**	14 ml	0,28 mg/ml	Not recommended
35 mg for moderate hepatic impairment (from one 70 mg vial)	5 ml	0,14 mg/ml	0,34 mg/ml

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

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

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS (CASCAGIN 70)

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)

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

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 to room temperature.
3. Aseptically add 10,5 ml of water for injection.
    a. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.
    b. This will give a final caspofungin concentration of 7,2 mg/ml per vial.
4. Remove the volume of CASCAGIN equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml) of reconstituted CASCAGIN 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 CASCAGIN 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 at refrigerated conditions (2 – 8 °C).

Preparation of the 50 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 50 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 to room temperature.
3. Aseptically add 10,5 ml of water for injection.
    a. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.
    b. This will give a final caspofungin concentration of 7,2 mg/ml per vial.
4. Remove the volume of CASCAGIN equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml) of reconstituted CASCAGIN 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 CASCAGIN 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 at refrigerated conditions (2 – 8 °C).

Preparation notes for CASCAGIN 70:

1. The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.
2. Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. DO NOT USE IF THE SOLUTION IS CLOUDY OR HAS PRECIPITATED.
3. CASCAGIN 70 is formulated to provide the full labeled vial dose (70 mg) when 10 ml is withdrawn from the vial.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

52/20.2.2/0245

52/20.2.2/0246

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 September 2021

10. DATE OF REVISION OF THE TEXT

To be confirmed.