FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CASPOLYN 50 (powder for concentrate for solution for infusion)

CASPOLYN 70 (powder for concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of **CASPOLYN 50** contains 50 mg caspofungin, equivalent to 55,5 mg caspofungin acetate.

Each vial of **CASPOLYN 70** contains 70 mg caspofungin equivalent to 77,7 mg caspofungin acetate.

CASPOLYN 50: After reconstitution, each mL of suspension contains 5,2 mg caspofungin.

CASPOLYN 70: After reconstitution, each mL of suspension contains 7,2 mg caspofungin.

Contains sugar:

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

A White to off white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Initial : 

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

CASPOLYN is indicated in adults for:

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

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

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

4.2 Posology and method of administration

General Recommendations in Adult Patients

CASPOLYN should be administered in adults (≥ 18 years of age) by slow intravenous infusion over approximately 1 hour.

Empirical therapy

Initial :

A single 70 mg loading dose should be administered on Day 1 followed by 50 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. If the 50 mg is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. Although an increase in efficacy with 70 mg daily has not been demonstrated, safety data suggest that an increase in dose to 70 mg daily is well tolerated.

Invasive Candidiasis

A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment of invasive candidiasis should be dictated by the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. Patients who remain persistently neutropenic may warrant a longer course of therapy pending resolution of the neutropenia.

The safety and efficacy of multiple doses up to 150 mg daily (range: 1 to 51 days; median: 14 days) have been studied in 100 adult patients with invasive candidiasis. Caspofungin, as contained in **CASPOLYN** was generally well tolerated in these patients receiving caspofungin at this higher dose; however, the efficacy of caspofungin at this higher dose was generally similar to patients receiving the 50 mg daily dose of caspofungin.

Oesophageal and Oropharyngeal Candidiasis

Fifty (50) mg should be administered daily.

Invasive Aspergillosis

A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. The efficacy of 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.

No dosage adjustment is necessary for elderly patients (65 years of age or more). No dosage adjustment is necessary based on gender, race or renal impairment.

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

Patients with Hepatic Insufficiency

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

Paediatric Patients

CASPOLYN should be administered in children and adolescents (3 months to 17 years of age) by slow IV infusion over approximately 1 hour. Dosing in children and adolescents (3 months to 17 years of age) should be based on the patient's body surface area (see "INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS, [1]Mosteller Formula"). For all indications, a single 70 mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualised to the indication, as described for each indication in adults (see General Recommendations in Adult Patients).

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

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

When **CASPOLYN** is co-administered to paediatric patients with inducers of medicine clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine, use of a **CASPOLYN** dose of 70 mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

Method of administration

After reconstitution and dilution, **CASPOLYN** should be administered by slow intravenous infusion over approximately 1 hour.

Reconstitution and instructions for use:

See section 6.6 for the reconstitution of **CASPOLYN** and instructions for use in adults and paediatric patients.

4.3 Contraindications

- **CASPOLYN** is contra-indicated in patients with hypersensitivity to caspofungin or any other component of this product (see section 6.1)
- **CASPOLYN** has not been studied in severe hepatic insufficiency.

4.4 Special warnings and precautions for use

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

Anaphylaxis has been reported during administration of caspofungin, as contained in **CASPOLYN**. If this occurs, **CASPOLYN** 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.

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.

Concomitant use of caspofungin with ciclosporin has been evaluated in healthy adult volunteers and in adult patients. Some healthy adult volunteers who received two 3 mg/kg doses of ciclosporin with caspofungin showed transient increases in alanine transaminase (ALT) and aspartate transaminase (AST) of less than or equal to 3-fold the upper limit of normal (ULN) that resolved with discontinuation of the treatment. 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. These data suggest that **CASPOLYN** can be used in patients receiving ciclosporin when the potential benefit outweighs the potential risk. Close monitoring of liver enzymes should be considered if **CASPOLYN** and ciclosporin are used concomitantly.

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).

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and paediatric patients treated with caspofungin. In some adult and paediatric patients with serious underlying conditions who

Initial : 

were receiving multiple concomitant medications with caspofungin, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported; a causal relationship to caspofungin has not been established. Patients who develop abnormal liver function tests during **CASPOLYN** therapy should be monitored for evidence of worsening hepatic function.

Cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post-marketing use of caspofungin, as contained in **CASPOLYN**. Caution should apply in patients with history of allergic skin reaction (see section 4.8).

CASPOLYN contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Studies *in vitro* show that caspofungin, as contained in **CASPOLYN** 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 substances. 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 medicinal products in pharmacological and clinical studies (see below).

In two clinical studies performed in healthy adult subjects, ciclosporin A (one 4 mg/kg dose or two 3 mg/kg doses 12hours apart) increased the AUC of caspofungin by approximately 35 %. These AUC increases are probably due to reduced uptake of caspofungin by the liver. Caspofungin did not increase the plasma levels of 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 caspofungin and ciclosporin were co-administered, that resolved with discontinuation of the medicinal products. 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 medicinal products are used concomitantly.

Caspofungin reduced the trough 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.

Clinical studies in healthy adult volunteers show that the pharmacokinetics of caspofungin are not altered to a clinically relevant extent by itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus. Caspofungin did not influence the pharmacokinetics of amphotericin B, itraconazole, rifampicin or mycophenolate mofetil. Although safety data are limited it appears that no special precautions are needed when amphotericin B, itraconazole, nelfinavir or mycophenolate mofetil are co-administered with caspofungin.

Rifampicin caused a 60 % increase in AUC and 170 % increase in trough concentration of caspofungin on the first day of co-administration when both medicinal products were initiated together in healthy adult volunteers. Caspofungin trough levels gradually decreased upon repeated administration. After two weeks' administration rifampicin had limited effect on AUC, but trough levels were 30 % lower than in adult subjects who received caspofungin alone. The mechanism of interaction could possibly be due to an initial inhibition and subsequent induction of transport proteins. A similar effect could be expected for other medicinal products that induce metabolic enzymes. Limited data from population pharmacokinetics studies indicate that concomitant use of caspofungin with the inducers efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin, or carbamazepine may result in a decrease in caspofungin AUC. When co-administering inducers of metabolic enzymes, an increase in the daily dose of caspofungin to 70 mg, following the 70 mg loading dose, should be considered in adult patients (see section 4.2).

All adult medicine interaction studies described above were conducted at a 50 or 70 mg daily caspofungin dose. The interaction of higher doses of caspofungin with other medicinal products has not been formally studied.

In paediatric patients, results from regression analyses of pharmacokinetic data suggest that co-administration of dexamethasone with caspofungin may result in clinically meaningful reductions in caspofungin trough concentrations. This finding may indicate that paediatric patients will have similar reductions with inducers as seen in adults. When caspofungin is co-administered to paediatric patients (12 months to 17 years of age) with inducers of medicine clearance, such as rifampicin, efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, a caspofungin dose of 70-mg/m^2 daily (not to exceed an actual daily dose of 70 mg) should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of caspofungin in pregnant women. **CASPOLYN** should not be used during pregnancy. Animal studies have shown developmental toxicity. Caspofungin has been shown to cross the placental barrier in animal studies.

Breastfeeding

It is unknown whether caspofungin is excreted in human milk. Available pharmacodynamic/ toxicological data in animals have shown excretion of caspofungin in milk. Women receiving **CASPOLYN** should not breastfeed.

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

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

No studies on the effects on the ability to drive and use machines have been performed. However, **CASPOLYN** may cause dizziness, somnolence and blurred vision, which may influence the ability to perform these activities. Patients should be warned not to drive or operate machinery until they are aware of the measure to which **CASPOLYN** affects them or until such side effects subside.

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

b. Tabulated list of adverse reactions

The following adverse reactions were reported during clinical studies and/or post-marketing use:

Table 1: ADRs reported during clinical studies and/or post-marketing use:

SYSTEM ORGAN CLASS	**INCIDENCE**	**ADVERSE REACTION**
Blood and lymphatic system disorders	Frequent	haemoglobindecreased,haematocritdecreased, whiteblood cell countdecreased
	Less frequent	anaemia, thrombocytopaenia, coagulopathy,leukopaenia, eosinophil count increased, plateletcount decreased, platelet count increased,lymphocyte count decreased, white blood cell countincreased, neutrophil count decreased
	Frequent	hypokalaemia

Initial :

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

Metabolism and nutrition disorders	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, hypoaesthesia
Eye disorders	Less frequent	ocular icterus, vision blurred, eyelid oedema,lacrimation increased
Cardiac disorders	Less frequent	palpitations, tachycardia, arrhythmia, atrialfibrillation, cardiac failure congestive
Vascular disorders	Frequent	phlebitis
	Less frequent	thrombophlebitis, flushing, hot flush, hypertension,hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	dyspnoea
	Less frequent	nasal congestion, pharyngolaryngeal pain,tachypnoea, bronchospasm, cough, dyspnoeaparoxysmal nocturnal, hypoxia, rales, wheezing
Gastrointestinal disorders	Frequent	nausea, diarrhoea,vomiting
	Less frequent	abdominal pain, abdominal pain upper, dry mouth,dyspepsia, stomach discomfort, abdominaldistension, ascites, constipation, dysphagia,flatulence

Initial : 

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

Hepatobiliary disorders	Frequent	elevated liver values(alanineaminotransferase,aspartateaminotransferase, blood alkalinephosphatase,bilirubin conjugated,blood bilirubin)
	Less frequent	cholestasis, hepatomegaly, hyperbilirubinaemia,jaundice, hepatic function abnormal, hepatotoxicity liver disorder, gammaglutamyltransferase increased
Skin and subcutaneous tissue disorders	Frequent	rash, pruritus,erythema,hyperhidrosis
	Less frequent	erythema multiforme, rash macular, rash maculo-papular, rash pruritic, urticaria, dermatitis allergic,pruritus generalised, rash erythematous, rashgeneralised, rash morbilliform, skin lesion
	Frequency unknown	Toxic epidermalnecrolysis andStevens-Johnsonsyndrome (seesection 4.4)
Musculoskeletal and connective tissue disorders	Frequent	arthralgia
	Less frequent	back pain, pain in extremity, bone pain, musculartweakness, myalgia
Renal and urinary disorders	Less frequent	renal failure, renal failure acute
General disorders and administration site conditions	Frequent	pyrexia, chills,infusion-site pruritus
	Less frequent	pain, catheter site pain, fatigue, feeling cold, feelinghot, infusion site erythema, infusion site induration,infusion site pain, infusion site swelling, injectionsite phlebitis, oedema

Initial :

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

		peripheral, tenderness, chestdiscomfort, chest pain, face oedema, feeling ofbody temperature change, induration, infusion siteextravasation, infusion site irritation, infusion sitephlebitis, infusion site rash, infusion site urticaria,injection site erythema, injection site oedema,injection site pain, injection site swelling, malaise,oedema
Investigations	Frequent	blood potassiumdecreased, bloodalbumin decreased
	Less frequent	blood creatinine increased, red blood cells urinepositive, protein total decreased, protein urinepresent, prothrombin time prolonged, prothrombintime shortened, blood sodium decreased, bloodsodium increased, blood calcium decreased, bloodcalcium increased, blood chloride decreased, bloodglucose increased, blood magnesium decreased,blood phosphorus decreased, blood phosphorusincreased, blood urea increased, activated partialthromboplastin time prolonged, blood bicarbonatedecreased, blood chloride increased, bloodpotassium increased, blood pressure increased,blood uric acid decreased, blood urine present,breath sounds abnormal, carbon dioxidedecreased, immunosuppressant medicine level increased, international normalised ratio increased,urinary casts, white blood cells urine positive, andpH urine increased.

c. Description of selected adverse reactions

Paediatric Patients

Initial : 

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

Data from studies completed in paediatric patients suggest that the overall incidence of clinical adverse experiences (26.3 %; 95 % CI -19.9, 33.6) is not worse than reported for adults treated with caspofungin (43.1 %; 95 %CI -40.0, 46.2). However, paediatric patients probably have a different adverse event profile compared to adult patients. The most common medicine-related clinical adverse experiences reported in paediatric patients treated with caspofungin were pyrexia (11.7 %), rash (4.7 %) and headache (2.9 %).

The following adverse reactions were reported:

SYSTEM ORGAN CLASS	**INCIDENCE**	**ADVERSE REACTION**
Blood and lymphatic system disorders	Frequent	eosinophil count increased
Nervous system disorders	Frequent	headache
Cardiac disorders	Frequent	tachycardia
Vascular disorders	Frequent	flushing, hypotension
Hepatobiliary disorders	Frequent	elevated liver enzyme levels (AST, ALT)
Skin and subcutaneous tissue disorders	Frequent	rash, pruritus
General disorders and administration site conditions	Frequent	chills, catheter site pain
Investigations	Frequent	decreased potassium, hypomagnesemia, increased glucose, decreased phosphorus, and increased phosphorus

Initial :

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 Reactions 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, which was administered as a single dose to 6 adult healthy subjects, and was generally well tolerated. In addition, a dose of 150 mg once daily up to 51 days has been administered to 100 adult patients and was generally well tolerated. 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 (echino**CASPOLYN**) compound synthesised from a fermentation product of Glarea lozoyensis. 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 branchpoints where cell growth and division occur.

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

5.2 Pharmacokinetic properties

Distribution

Caspofungin is extensively bound to albumin. The unbound fraction of caspofungin in plasma varies from 3.5 % in healthy volunteers to 7.6 % in patients with invasive candidiasis. Distribution plays the prominent role in caspofungin plasma pharmacokinetics and is the rate-controlling step in both the alpha- and beta-disposition phases. 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 of caspofungin is currently impossible to obtain.

Biotransformation

Caspofungin undergoes spontaneous degradation to an open ring compound. Further metabolism involves peptide hydrolysis and N-acetylation. 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. *In vitro* studies show that caspofungin is not an inhibitor of cytochrome P450 enzymes 1A2, 2A6, 2C9, 2C19, 2D6 or3A4. In clinical studies, caspofungin did not induce or inhibit the CYP3A4 metabolism of other medicinal products. 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. 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. An additional gamma-phase also occurs with a half-life of 45 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance.

Initial : 

Approximately 75 % of a radioactive dose was recovered during 27 days: 41 % in urine and 34 % in faeces. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration. Excretion is slow and the terminal half-life of radioactivity was 12 to 15 days. A small amount of caspofungin is excreted unchanged in urine (approximately 1.4 % of dose).

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

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

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 (see section 4.2).

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 <10ml/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 17-38 % higher in women than in men.

Elderly: A modest increase in AUC (28 %) and C_{24h} (32 %) was observed in elderly male subjects compared with young male subjects. In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients.

Race: Patient pharmacokinetic data indicated that no clinically significant differences in the pharmacokinetics of caspofungin were seen among Caucasians, Blacks, Hispanics, and Mestizos.

Paediatric Patients:

In adolescents (ages 12 to 17 years) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ was generally comparable to that seen in adults receiving caspofungin at 50 mg daily. All adolescents received doses >50 mg daily, and, in fact, 6 of 8 received the maximum dose of 70 mg/day. The caspofungin plasma concentrations in these adolescents were reduced relative to adults receiving 70 mg daily, the dose most often administered to adolescents.

In children (ages 2 to 11 years) receiving caspofungin at 50 mg/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.

In young children and toddlers (ages 12 to 23 months) receiving caspofungin at 50 mg/m^2 daily (maximum 70 mg daily), the caspofungin plasma $AUC_{0\text{-}24hr}$ after multiple doses was comparable to that seen in adults receiving caspofungin at50 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 0-24hr 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.

In neonates and infants (<3 months) receiving caspofungin at 25 mg/m^2 daily (corresponding mean daily dose of 2,1 mg/kg), caspofungin peak concentration ($C_{1\ hr}$) and caspofungin trough concentration ($C_{24\ hr}$) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, $C_{1\ hr}$ was comparable and $C_{24\ hr}$ modestly elevated (36 %) in these neonates and infants relative to adults. However, variability was seen in both $C_{1\ hr}$ (Day 4 geometric mean 11,73 µg/ml, range 2,63 to 22,05 µg/ml) and $C_{24\ hr}$ (Day 4 geometric mean 3,55 µg/ml, range 0,13 to 7,17 µg/ml). $AUC_{0\text{-}24hr}$ measurements were not performed in this study due to the sparse plasma sampling. Of note, the efficacy and safety of caspofungin have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Mannitol

Glacial acetic acid

Sodium hydroxide

Nitrogen

6.2 Incompatibilities

Do not mix with diluents containing glucose, as **CASPOLYN** is not stable in diluents containing glucose. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

Reconstituted concentrate: should be used 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 patient infusion solution: should be used immediately. Stability data have shown that the product 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 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.

CASPOLYN contains no 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 would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution and dilution have taken place in controlled validated aseptic conditions.

6.4 Special precautions for storage

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

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

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

6.5 Nature and contents of container

Caspofungin 50 mg and 70 mg powders container consist of 10 R (10 ml) Type I glass vial with a grey bromobutyl rubber stopper and a flip-off seal with a plastic cap.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution of CASPOLYN

DO NOT USE ANY DILUENTS CONTAINING DEXTROSE (alpha-D-GLUCOSE), as **CASPOLYN** is not stable in diluents containing dextrose.

DO NOT MIX OR CO-INFUSE **CASPOLYN** WITH ANY OTHER MEDICATIONS, as there is no data available on the compatibility of **CASPOLYN** with other intravenous substances, additives or medications. Visually inspect the infusion solution for particulate matter or discolouration.

INSTRUCTIONS FOR USE IN ADULTS

Step 1. Reconstitution of vials

To reconstitute the powdered medicine, bring the refrigerated vial of **CASPOLYN** to room temperature and aseptically add 10,5 ml of Sterile Water for Injection. The concentrations of the reconstituted vials will be: 7,2 mg/ml (70 mg vial) or 5,2 mg/ml (50 mg vial).

The white to off-white compact powder will dissolve completely. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually inspected for particulate matter or discolouration. This reconstituted solution may be stored for up to 24 hours at or below 25 °C.

Step 2. Addition of Reconstituted CASPOLYN to patient infusion solution

Initial : 

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

Diluents for the final patient infusion solutions are: Sterile Saline for Injection or Lactated Ringer's Solution. The standard patient infusion is prepared by aseptically adding the appropriate amount of reconstituted medicine (as shown in the table below) to a 250 ml intravenous bag or bottle. Reduced volume infusions in 100 ml may be used, when medically necessary, for 50 mg or 35 mg daily doses. Do not use if the solution is cloudy or 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. **CASPOLYN** should be administered by slow intravenous infusion over approximately 1 hour.

PREPARATION OF THE PATIENT INFUSION SOLUTIONS IN ADULTS

DOSE*	**Volume of reconstituted CASPOLYN for transfer to intravenous bag or bottle**	**Standard preparation (reconstituted CASPOLYN added to 250 ml) final concentration**	**Reduced volume infusion (reconstituted CASPOLYN 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	5 ml	0,14 mg/ml	0,34 mg/ml

Initial : 

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

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

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

INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS

Calculation of Body Surface Area (BSA) for paediatric dosing

Before preparation of infusion, calculate the body surface area (BSA) of the patient using the following formula (Mosteller Formula):

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

Preparation of the 70 mg/m^2 infusion for paediatric patients > 3 months of age (using a 70 mg vial)

1. Determine the actual loading dose to be used in the paediatric patient by using the patient's BSA (as calculated above) and the following equation: BSA (m^2) X 70 mg/m^2 = Loading Dose

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

2. Equilibrate the refrigerated vial of **CASPOLYN** to room temperature.

3. Aseptically add 10,5 ml of Sterile Water for Injection. [a]This reconstituted solution may be stored for up to 24 hours at 25 °C. [b]This will give a final caspofungin concentration in the vial of 7,2 mg/ml.

4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted **CASPOLYN** to an IV bag (or bottle) containing 250 ml of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection. Alternatively, the volume (ml)[c] of reconstituted **CASPOLYN** 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/m^2 infusion for paediatric patients > 3 months of age (using a 50 mg vial)]".** The final caspofungin concentration in the 50 mg vial after reconstitution is 5,2 mg/ml.

Preparation of the 50 mg/m^2 infusion for paediatric patients > 3 months of age (using a 50 mg vial)

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

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

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

2. Equilibrate the refrigerated vial of **CASPOLYN** to room temperature.

3. Aseptically add 10,5 ml of Sterile Water for Injection. [a]This reconstituted solution may be stored for up to 24 hours at or below 25 °C. [b]This will give a final caspofungin concentration in the vial of 5,2 mg/ml.

4. Remove the volume of medicine equal to the calculated loading dose (Step 1) from the vial. Aseptically transfer this volume (ml)[c] of reconstituted **CASPOLYN** to an IV bag (or bottle) containing 250 ml of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection or Lactated Ringer's Injection. Alternatively, the volume (ml)c of reconstituted **CASPOLYN** 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 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/m^2 infusion for paediatric patients > 3 months of age (using a 70 mg vial)]"**. The final caspofungin concentration in the 70 mg vial after reconstitution is 7,2 mg/ml.

Preparation notes

a: The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

b: Visually inspect the reconstituted solution for particulate matter or discolouration during reconstitution and prior to infusion. Do not use solution if cloudy or has precipitated.

c: **CASPOLYN** is formulated to provide the full labelled vial dose (70 mg or 50 mg) when 10 ml is withdrawn from the vial.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2

6 Coombe Place,

Rivonia,

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

CASPOLYN 50 : 55/20.2.2/0831

CASPOLYN 70 : 55/20.2.2/0832

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 June 2024

FINAL PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

10. DATE OF REVISION OF THE TEXT

04 June 2024

Initial :