SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)

CASFOLRED 50 (lyophilised powder for concentrate for solution for infusion)

CASFOLRED 70 (lyophilised powder for concentrate for solution for infusion)

COMPOSITION

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

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

The other ingredients of **CASFOLRED** are argon, glacial acetic acid, mannitol, sodium hydroxide, sucrose and water for injection.

Contains mannitol.

PHARMACOLOGICAL CLASSIFICATION

A 20.2.2. Antimicrobial (chemotherapeutic agents): Fungicides

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Caspofungin acetate is a water-soluble, semi-synthetic lipopeptide (echinocandin) 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* and *Aspergillus* species.

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.

Resistance

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

A caspofungin MIC of ≤ 2 mcg/ml using the CSLI M27-A3 method indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved; there is insufficient treatment outcome information on isolates with reduced caspofungin susceptibility to define categories other than susceptible. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations > 2 mcg/ml for growth inhibition have developed in a mouse model of *C. albicans* infection and in some patients with *Candida* infections. Some of these isolates had mutations in the FKS1 gene.

Development of *in vitro* resistance to caspofungin by *Aspergillus* species has not been identified. In clinical experience, resistance in patients with invasive aspergillosis has not been observed. The incidence of resistance in various clinical isolates of *Candida* and *Aspergillus* species is unknown.

Pharmacokinetic properties

Distribution

Plasma concentrations of caspofungin decline in a polyphasic manner after intravenous infusions. A short alpha-phase occurs immediately post-infusion, which is followed by a beta-phase with a half-life of 9 to 11 hours. An additional longer gamma-phase also occurs with a

half-life of 40 to 50 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance.

Caspofungin is highly protein bound (approximately 97 %), and distribution to 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 [3H] caspofungin acetate. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration. Plasma clearance of caspofungin is dependent on distribution rather than on biotransformation or excretion.

Metabolism

There is a slow metabolism of caspofungin by hydrolysis and N-acetylation. Caspofungin also undergoes spontaneous chemical degradation to an open ring peptide compound, forming two reactive intermediate products. 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 studies conducted, approximately 75 % of the radioactivity was recovered of which 41 % was 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. A small amount of caspofungin (approximately 1,4 % of dose) is excreted unchanged in urine. Renal clearance of parent substance is low (approximately 0,15 ml/min).

Special populations

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 old] and children [2 to 11 years old] followed by a study in younger patients [3 to 23 months old] and then followed by a study in neonates and infants [< 3 months]).

- In adolescents (ages 12 to 17 years old) 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 old) 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, it should be recognised that the AUC values in these children on Day 1 were still less than those seen in adults at steady-state conditions.
- In young children and toddlers (ages 3 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. As in the older children, these young children who received 50 mg/m^2 daily had slightly higher $AUC_{0\text{-}24hr}$ values on Day 1 relative to adults receiving the standard 50 mg daily dose. The caspofungin pharmacokinetic results from the young children (3 to 23 months of age) that received 50

mg/m^2 caspofungin daily were similar to the pharmacokinetic results from older children (2 to 11 years old) that received the same dosing regimen.

- In neonates and infants (< 3 months) receiving caspofungin at 25 mg/m^2 daily, caspofungin peak concentration (C_{1hr}) and caspofungin trough concentration (C_{24hr}) after multiple doses were comparable to that seen in adults receiving caspofungin at 50 mg daily. On Day 1, C_{1hr}, was comparable and C_{24hr} modestly elevated (36 %) in these neonates and infants relative to adults. $AUC_{0\text{-}24hr}$ measurements were not performed in this study due to the sparse plasma sampling. 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.

Hepatic impairment:

Plasma concentrations of caspofungin after a single 70 mg dose in 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 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. Caspofungin has not been studied in severe hepatic insufficiency.

Gender:

The caspofungin plasma concentration in some women was elevated approximately 20 % relative 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).

INDICATIONS

CASFOLRED is indicated 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 patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and itraconazole.

Paediatric Use

The safety and effectiveness of **CASFOLRED** in paediatric patients 3 months to 17 years old are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in paediatric patients and additional data from studies in patients 3 months to 17 years old. The efficacy and safety of **CASFOLRED** have not been adequately studied in prospective clinical trials involving neonates and infants under 3 months of age.

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

CONTRAINDICATIONS

- **CASFOLRED** is contraindicated in patients with a hypersensitivity to caspofungin or to

any of the excipients.

- **CASFOLRED** has not been studied in patients with severe hepatic insufficiency.

WARNINGS AND SPECIAL PRECAUTIONS

Anaphylaxis has been reported during administration of **CASFOLRED**. Should this occur, **CASFOLRED** should be discontinued and appropriate treatment administered. Possible histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment.

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

In adult patients with mild and moderate hepatic impairment, the AUC is increased about 20 % and 75 %, respectively. It is recommended for adults with moderate hepatic impairment that the daily dose be reduced to 35 mg. 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 **CASFOLRED** should be used with caution in these patients (see CONTRAINDICATIONS, DOSAGE AND DIRECTIONS and Pharmacokinetic properties).

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and adult and paediatric patients treated with **CASFOLRED**. In some adult and paediatric patients with serious underlying **CASFOLRED** conditions who were receiving multiple concomitant medicines with **CASFOLRED**, cases of clinically significant hepatic dysfunction, hepatitis and hepatic failure have been reported. A causal relationship to **CASFOLRED** has not been established. Patients who develop abnormal liver function tests during **CASFOLRED** therapy should be

monitored for evidence of worsening hepatic function and the risk/benefit of continuing **CASFOLRED** therapy.

Cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post-marketing use of **CASFOLRED**. Caution should apply in patients with history of allergic skin reactions (see SIDE EFFECTS).

The use of **CASFOLRED** with 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. Close monitoring of liver enzymes should be considered.

There was also an increase of approximately 35 % in the area under the curve (AUC) of **CASFOLRED** when co-administered with ciclosporin; blood levels of ciclosporin remained unchanged.

CASFOLRED decreased the 12 hour blood concentration (C12hr) of tacrolimus (FK-506) by 26 % in healthy adult volunteers. For patients who are concomitantly treated with tacrolimus, blood concentrations have to be monitored and appropriate dosage adjustments of tacrolimus should be considered.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

CASFOLRED contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use **CASFOLRED.**

CASFOLRED contains mannitol which, on rare occasions, may cause hypersensitivity reactions.

INTERACTIONS

In vitro studies have shown that caspofungin is not an inhibitor of any enzyme in the cytochrome P450 (CYP) system. Clinical studies have shown that 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.

In vitro and *in vivo* studies of caspofungin in combination with amphotericin B, does not result in antagonism of antifungal activity against either *A. fumigatus* or *C. albicans*. Results from *in vitro* studies suggest that there was some evidence of additive/indifferent or synergistic activity against *A. fumigatus* and additive/indifferent activity against *C. albicans*. The clinical significance of these results is unknown.

In two adult clinical studies, ciclosporin (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by about 35 %. The AUC increases are probably due to reduced uptake of caspofungin by liver. **CASFOLRED** did not increase the plasma levels of ciclosporin. There were transient increases in liver ALT and AST when **CASFOLRED** and ciclosporin were co-administered. (See WARNINGS AND SPECIAL PRECAUTIONS).

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

CASFOLRED decreased the 12 hour blood concentration (C_{12hr}) of tacrolimus (FK-506) by 26 % in healthy adult volunteers. For patients who are concomitantly treated with tacrolimus, blood concentrations have to be monitored and appropriate dosage adjustments of tacrolimus should be considered.

Two clinical interaction studies indicate that rifampicin induces and inhibits caspofungin

disposition with net induction at a steady state. Additionally results from population pharmacokinetic screening in adults suggest that co-administration of **CASFOLRED** with other inducers of medicine clearance (such as efavirenz, nevirapine, phenytoin, dexamethasone or carbamazepine) 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 **CASFOLRED** 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 **CASFOLRED** should be considered (see DOSAGE AND DIRECTIONS FOR USE).

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

PREGNANCY AND LACTATION

There are no data on the use of **CASFOLRED** in pregnant women, therefore, **CASFOLRED** should not be used during pregnancy.

It is not known if **CASFOLRED** is excreted in the breast milk of humans, therefore, breast-feeding is not recommended.

DOSAGE AND DIRECTIONS

Adults (≥ 18 years of age):

CASFOLRED should be administered by a slow infusion over approximately 1 hour.

Empirical therapy

A single 70 mg loading dose should be administered on Day 1, thereafter followed by 50 mg daily. The patient's clinical response should determine the duration of treatment. Empirical therapy should be continued until the neutropenia is resolved. 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 50 mg is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. Even though 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 tolerated.

Invasive Candidiasis

A single 70 mg loading dose should be administered on Day 1, followed thereafter by 50 mg daily. Duration of treatment of invasive candidiasis should be determined 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 require a longer course of therapy until the 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. **CASFOLRED** is generally well tolerated in these patients receiving **CASFOLRED** at this higher dose. The efficacy of **CASFOLRED** at this higher dose is generally similar to patients receiving the 50 mg daily dose.

Oesophageal and Oropharyngeal Candidiasis

50 mg should be given daily.

Invasive Aspergillosis

A single 70 mg loading dose should be administered on Day 1, followed thereafter by 50 mg daily. 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 dose adjustments are necessary for elderly patients (65 years of age or more).

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

When **CASFOLRED** is co-administered with the metabolic inducers such as efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine, use of a daily dose of 70 mg of **CASFOLRED** should be considered (see INTERACTIONS).

Patients with Hepatic Impairment

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) do not need a dosage adjustment (see CONTRAINDICATIONS).

For adult patients with moderate hepatic insufficiency (Child-Pugh-score 7 to 9), **CASFOLRED** 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 patients with severe hepatic insufficiency (Child-Pugh score > 9) and in paediatric patients with any degree of hepatic insufficiency (see CONTRAINDICATIONS).

Paediatric Patients

CASFOLRED should be administered in children and adolescents (3 months to 17 years old) by slow IV infusion over approximately 1 hour. Dosing in children and adolescents (3 months to 17

years old) should be based on the patient's body surface area (see INSTRUCTIONS FOR USE IN PAEDIATRIC PATIENTS, Mosteller[1] Formula). For all indications, a single 70 mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily). Duration of treatment should be individualised to the indication, as described for each indication in adults.

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

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

Reconstitution of CASFOLRED

CASFOLRED is not stable in diluents containing dextrose.

DO NOT USE ANY DILUENTS CONTAINING DEXTROSE (ALPHA-D-GLUCOSE).

DO NOT MIX OR CO-INFUSE **CASFOLRED** WITH ANY OTHER MEDICATIONS, since no data is available on the compatibility of **CASFOLRED** with other intravenous substances, additives or medications.

Visually inspect the infusion solution for particulate matter or discolouration.

INSTRUCTION FOR USE IN ADULTS

Step 1. Reconstitution of vials

To reconstitute **CASFOLRED** powder, bring the refrigerated vial of **CASFOLRED** to room temperature and aseptically add 10,5 ml of either 0,9 % Sodium Chloride Injection, Sterile Water

for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0,9 % benzyl alcohol. The reconstituted product is stable for a period of 1 hour.

The concentrations of the reconstituted vials will be: 5,2 mg/ml (50 mg vial) or 7,2 mg/ml (70 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.

Step 2. Addition of Reconstituted CASFOLRED 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 drug (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.

Although chemical and physical stability of reconstituted/diluted solutions has been demonstrated for 24 hours at 25 °C and 48 hours at 2 to 8 °C 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/dilution has taken place in controlled and validated aseptic conditions.

CASFOLRED should be administered by slow intravenous infusion over approximately 1 hour.

PREPARATION OF THE PATIENT INFUSION SOLUTIONS

Dose*	Volume of reconstituted CASFOLRED for transfer to intravenous bag or bottle	Standard preparation (Reconstituted CASFOLRED added to 250 ml) final concentration.	Reduced volume infusion (Reconstituted CASFOLRED added to 100 ml) final concentration.
35 mg for moderate hepatic insufficiency (from one 50 mg vial)	7 ml	0,14 mg/ml	0,34 mg/ml
35 mg for moderate hepatic insufficiency (from one 70 mg vial)	5 ml	0,14 mg/ml	0,34 mg/ml
50 mg	10 ml	0,20 mg/ml	0,47 mg/ml
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
* 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 the 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 50 mg/m^2 infusion for paediatric patients > 3 months of age (using a 50 mg vial)

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

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

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

2. Bring the refrigerated vial of **CASFOLRED** to room temperature.

3. Aseptically add 10,5 ml of 0,9 % Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben or Bacteriostatic Water for Injection with 0,9 % benzyl alcohol.

[a] This reconstituted solution may be stored for up to 24 hours at 25 °C.

[b] This will give a final **CASFOLRED** 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 **CASFOLRED** to an IV bag (or bottle)

containing 250 ml of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection, or Lactated Ringers Injection.

Alternatively, the volume (ml)[c] of reconstituted **CASFOLRED** 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.

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 **CASFOLRED** concentration in the 70 mg vial after reconstitution is 7,2 mg/ml.

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

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

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

   The maximum loading dose on Day 1 should not exceed 70 mg regardless of the patient's calculated dose.
2. Bring the refrigerated vial of **CASFOLRED** to room temperature.
3. Aseptically add 10,5 ml of 0,9 % Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection with methylparaben and propylparaben or Bacteriostatic Water for Injection with 0,9 % benzyl alcohol. This reconstituted solution may be stored for up to 24 hours at 25 °C[b]. This will give a final **CASFOLRED** 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 **CASFOLRED** to an IV bag (or bottle)

containing 250 ml of 0,9 %, 0,45 %, or 0,225 % Sodium Chloride Injection, or Lactated Ringers Injection. Alternatively, the volume (ml)[c] of reconstituted **CASFOLRED** 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.

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 **CASFOLRED** concentration in the 50 mg vial after reconstitution is 5,2 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] **CASFOLRED** is formulated to provide the full labelled vial dose (50 mg or 70 mg) when 10 ml is withdrawn from the vial.

SIDE-EFFECTS

The following side effects were reported for adult patients:

Blood and lymphatic system disorders

- *Frequent:* haemoglobin decreased, haematocrit decreased, white blood cell count decreased.
- *Less frequent:* anaemia, thrombocytopenia, coagulopathy, leukopenia, eosinophil count increased, platelet count decreased, platelet count increased, lymphocyte count decreased, white blood cell count increased, neutrophil count decreased.

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, hypoaesthesia.

Eye disorders

- *Less frequent:* ocular icterus, vision blurred, eyelid oedema, lacrimation increased.

Cardiac disorders

- *Less frequent:* palpitations, tachycardia, dysrhythmia, atrial fibrillation, 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, dyspnoea paroxysmal nocturnal, hypoxia, rales, wheezing.

Gastrointestinal disorders

- *Frequent:* nausea, vomiting, diarrhoea.
- *Less frequent:* abdominal pain, abdominal pain upper, dry mouth, dyspepsia, stomach discomfort, abdominal distension, ascites, constipation, dysphagia, flatulence.

Hepatobiliary disorders

- *Frequent:* elevated liver values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, bilirubin conjugated, blood bilirubin).
- *Less frequent:* cholestasis, hepatomegaly, hyperbilirubinaemia, jaundice, hepatic function abnormal, hepatotoxicity, liver disorder, gamma-glutamyltransferase increased.

Skin and subcutaneous tissue disorders

- *Frequent:* rash, pruritus, hyperhidrosis, erythema.
- *Less frequent:* erythema multiforme, rash macular, rash maculo-papular, rash pruritic, urticaria, dermatitis allergic, pruritus generalised, rash erythematous, rash generalised, rash morbilliform, skin lesion.
- *Frequency unknown:* toxic epidermal necrolysis and Stevens-Johnson syndrome.

Musculoskeletal, connective tissue and bone disorders

- *Frequent:* arthralgia.
- *Less frequent:* back pain, pain in extremity, bone pain, muscular weakness, myalgia.

Renal and urinary disorders

- *Less frequent:* renal failure, renal failure acute.

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*: blood potassium decreased, 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 calcium decreased, blood calcium 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, and pH urine increased.

The following side effects were reported for paediatric patients:

Blood and lymphatic system disorders

- *Frequent*: increased eosinophil count.

Nervous system disorders

- *Frequent*: headache.

Cardiac disorders

- *Frequent*: tachycardia.

Vascular disorders

- *Frequent*: flushing, hypotension.
- *Frequency unknown*: swelling and peripheral oedema.

Hepatobiliary disorders

- *Frequent:* elevated liver enzyme levels (AST, ALT).
- *Frequency unknown:* hepatic dysfunction.

Skin and subcutaneous tissue disorders

- *Frequent:* rash, pruritus.
- *Frequency unknown*: histamine-mediated symptoms (rash, facial swelling, pruritus, sensation of warmth, bronchospasm), anaphylaxis.

General disorders and administration site conditions

- *Frequent*: fever, chills, catheter-site pain.

Investigations

- *Frequent*: increased liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), decreased potassium, hypomagnesaemia, increased glucose, decreased phosphorus, increased phosphorus.
- *Frequency unknown*: hypercalcaemia, increased eosinophils.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In one study 210 mg was the highest dose which was administered as a single dose to 6 healthy subjects and in another study 150 mg once a day for up to 51 days was administered to 100 subjects.

CASFOLRED is not dialysable.

IDENTIFICATION

Unopened vials

Each vial of **CASFOLRED** contains a white to off white lyophilised cake/powder.

Reconstituted vials

Clear solution, essentially free from visible particles.

Diluted product for infusion

Clear solution, essentially free from visible particles.

PRESENTATION

CASFOLRED 50 is supplied in 10 ml USP type – I clear glass tubular Lyo vials with 20 mm neck diameter and 20 mm grey bromobutyl rubber stoppers and sealed with 20 mm aluminium flip off seals.

CASFOLRED 70 is supplied in 10 ml USP type – I clear glass tubular Lyo vials with 20 mm neck diameter and 20 mm grey bromobutyl rubber stoppers and sealed with 20 mm aluminium flip off seals.

The glass vial is packed in a printed outer carton along with the package insert.

STORAGE INSTRUCTIONS

Storage of unopened vials

Store at 2 °C to 8 °C.

Storage of reconstituted/diluted solution

Although chemical and physical stability of reconstituted/diluted solutions has been demonstrated for 24 hours at 25 °C and 48 hours at 2 to 8 °C 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/dilution has taken place in controlled and validated aseptic conditions.

Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

CASFOLRED 50: 50/20.2.2/0945

CASFOLRED 70: 50/20.2.2/0946

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd

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