SCHEDULING STATUS: **S4**

PROPRIETARY NAME (AND DOSAGE FORM):
FUNGIZONE INTRAVENOUS injection

COMPOSITION:

FUNGIZONE Intravenous (Amphotericin B for injection) is a sterile lyophilised powder providing 50 mg amphotericin B and 41 mg sodium desoxycholate with 20,2 mg sodium phosphate as a buffer, per vial. At the time of manufacture, the air in the container is replaced by nitrogen.

List of excipients: desoxycholic acid, disodium phosphate dodecahydrate, monosodium phosphate dihydrate, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

Category A 20.1.7 (Antifungal Antibiotics)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Microbiology:

Amphotericin B shows a high order of *in vitro* activity against many species of fungi. *Histoplasma capsulatum, Coccidioides immitis,* Candida species, *Blastomyces dermatitidis, Rhodotorula, Cryptococcus neoformans, Sporothrix schenckii, Mucor mucedo* and *Aspergillus fumigatus* are all inhibited by concentrations of amphotericin B ranging from 0,03 to 1,0 µg/ml *in vitro*. The antifungal is without effect on bacteria, rickettsiae and viruses.

Pharmacokinetic properties

Human Pharmacology:

Amphotericin B is fungistatic rather than fungicidal in concentrations obtainable in body fluids. It probably acts by binding to sterols in the fungal cell membrane of susceptible fungi with a resultant change in membrane permeability which allows leakage of intracellular components. Mammalian cell membranes also contain sterols and it has been suggested that the damage to human cells (toxicity) and damage to fungal cells (antifungal effect) may share common mechanisms.

Average peak blood levels of 0,5 to 2 µg/ml are found in adults given repeated doses of approximately 0,5 mg/kg/day. An elimination half-life of approximately 15 days follows an initial plasma half-life of about 24 hours. Amphotericin B circulating in plasma is highly bound (> 90 %) to plasma proteins and is poorly dialysable. Approximately two thirds of concurrent plasma concentrations have been detected in fluids from inflamed pleura, peritoneum, synovium, and acqueous humor. Concentrations in the cerebrospinal fluid seldom exceed 2,5 percent of those in the plasma or are non-detectable. Little amphotericin B penetrates into vitreous humor or normal amniotic fluid.

Amphotericin B is excreted very slowly (over weeks to months) by the kidneys with two to five percent of a given dose being excreted in the biologically active form.
After treatment is discontinued, the drug can be detected in the urine for at least seven weeks due to the slow disappearance of the medicine.

INDICATIONS:

FUNGIZONE Intravenous is indicated primarily in patients with progressive, potentially life-threatening fungal infections such as cryptococcosis (torulosis); North American blastomycosis; the disseminated forms of moniliasis (candidiasis), coccidioidomycosis and histoplasmosis; mucormycosis (phycomycosis) caused by susceptible species of the genera *Mucor, Rhizopus*, *Absidia, Entomophthora,* and *Basidiobolus*; sporotrichosis (*Sporothrix schenckii*); aspergillosis (*Aspergillus fumigatus*).
Amphotericin B may be helpful in the treatment of American mucocutaneous leishmaniasis, but is not the medicine of choice in primary therapy.

FUNGIZONE Intravenous should not be used to treat the common non-invasive fungal infections such as oral thrush, vaginal candidiasis and oesophageal candidiasis in patients with normal neutrophil counts.

CONTRAINDICATIONS:

FUNGIZONE Intravenous is contraindicated in patients who have shown hypersensitivity to it or any other component in the formulation unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to FUNGIZONE Intravenous therapy.

Paediatric Use:

Safety and effectiveness in paediatric patients have not been established through adequate and well-controlled studies.

Systemic fungal infections have been treated in paediatric patients without reports of unusual side effects.

WARNINGS and SPECIAL PRECAUTIONS:

FUNGIZONE Intravenous should be administered intravenously only, and be given to patients under close clinical supervision by medically trained personnel.

FUNGIZONE Intravenous should be used **primarily** for treatment of patients with progressive and potentially fatal fungal infections; it should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.

FUNGIZONE Intravenous may be the only effective treatment available for a potentially fatal disease.

In each case, therefore, its possible life saving effect must be balanced against its untoward and dangerous effects.

Hence, FUNGIZONE Intravenous should be used parenterally only in hospitalised patients or those under close clinical observation by medically trained personnel and should be reserved for those

patients in whom a diagnosis of the progressive, potentially fatal forms of susceptible mycotic infections has been made.

Exercise caution to prevent inadvertent FUNGIZONE Intravenous overdose, which can result in potentially fatal cardiac or cardio-respiratory arrest. **Verify the product name and dosage pre-administration, especially if the dose prescribed exceeds 1,5 mg/kg. (**See **DOSAGE AND DIRECTIONS FOR USE** and **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT.)**

Acute reactions including chills, fever, anorexia, nausea, vomiting, headache, myalgia, arthralgia, and hypotension are common when FUNGIZONE Intravenous is given intravenously.

Rapid intravenous infusion, over less than one hour, particularly in patients with renal insufficiency, has been associated with hyperkalaemia and arrhythmias, and should, therefore, be avoided (see **DOSAGE AND DIRECTIONS FOR USE**).

Leukoencephalopathy has been reported following use of FUNGIZONE Intravenous in patients who received total body irradiation.

Renal function and serum electrolytes (particularly magnesium, sodium and potassium) should be monitored frequently during FUNGIZONE Intravenous therapy.

Laboratory facilities must be available to perform blood urea nitrogen and serum creatinine or endogenous creatinine clearance tests. These determinations should be made at least weekly during therapy. If the blood urea nitrogen exceeds 40 mg per 100 ml or the serum creatinine exceeds 3,0 mg per 100 ml the medicine should be discontinued or the dosage markedly reduced until renal function is improved.

It is also advisable to monitor liver function, as well as weekly haemograms. Whenever medication is interrupted for a period longer than 7 days, therapy should be resumed by starting with the lowest dosage level, i.e. 0,25 mg/kg of body mass, and increased gradually as outlined under DOSAGE AND DIRECTIONS FOR USE.

Concomitant Medication:

Corticosteroids should not be administered concomitantly unless they are necessary to control sensitivity reactions. Other nephrotoxic antibiotics and antineoplastic agents such as nitrogen mustard should not be given concomitantly except with great caution.

Intolerance Therapy:

While some patients may tolerate full intravenous doses of FUNGIZONE Intravenous without difficulty, most will exhibit some intolerance, often at less than the full therapeutic dosage. They may be made less severe by giving aspirin, other antipyretics (e.g. paracetamol), antihistamines or antiemetics.
Pethidine (25 mg to 50 mg intravenously) has been used in some patients to decrease the duration or intensity of shaking chills and fever following FUNGIZONE Intravenous therapy.
Administration of the medicine on alternate days may decrease anorexia and phlebitis. Intravenous administration of small doses of adrenal corticosteroids just prior to or during the FUNGIZONE Intravenous infusion may decrease febrile reactions. The dosage and duration of such corticosteroid therapy should be kept to a minimum.
Adding a small amount of heparin to the infusion (1000 units per infusion), rotation of the injection site, and the use of a paediatric scalp-vein needle may lessen the incidence of thrombophlebitis.
Extravasation may cause chemical irritation.

INTERACTIONS:

When administered concurrently, the following medicines may interact with FUNGIZONE Intravenous:
Other nephrotoxic medication, such as cisplatin, pentamidine, aminoglycosides, and cyclosporine, may enhance the potential for renal toxicity, and thus should be used concomitantly only with great caution.

Corticosteroids, corticotropin (ACTH) and diuretics may potentiate amphotericin B-induced hypokalaemia (see **WARNINGS AND SPECIAL PRECAUTIONS**).
Agents whose effects or toxicity may be increased by hypokalaemia e.g. digitalis glycosides, skeletal muscle relaxants and antiarrhythmic agents.

Flucytosine - concomitant use may increase the toxicity of flucytosine possibly by increasing its cellular uptake and/or impairing its renal excretion.

Leukocyte transfusions - though not observed in all studies, acute pulmonary reactions have been observed in patients given FUNGIZONE Intravenous during or shortly after leukocyte transfusions, thus it is advisable to separate these infusions as far as possible and to monitor pulmonary function.

Imidazoles - (e.g. ketoconazole, itraconazole, miconazole, clotrimazole, fluconazole). *In vitro* studies and animal studies with the combination of FUNGIZONE Intravenous and imidazoles suggest that imidazoles may induce fungal resistance to FUNGIZONE Intravenous.

Combination therapy should be administered with caution, especially in immunocompromised patients.

PREGNANCY AND LACTATION:

Pregnancy

Safety of use in pregnancy has not been established.

Lactation

It is not known whether FUNGIZONE Intravenous is excreted in breastmilk. Mothers on FUNGIZONE Intravenous should therefore not breast-feed a baby.

DOSAGE AND DIRECTIONS FOR USE:

FUNGIZONE Intravenous should be administered by slow intravenous infusion. Intravenous infusion should be given over a period of approximately two to six hours observing the usual precautions for intravenous therapy. The recommended concentration for intravenous infusion is 0,1 mg/ml (1 mg/10 ml).

Dosage must be adjusted to the specific requirements of each patient since tolerance to FUNGIZONE Intravenous varies individually. Therapy is usually instituted with a daily dose of 0,25 mg/kg of body mass and gradually increased as tolerance permits.

Though not proven to be a reliable predictor of intolerance, an initial test dose (1 mg in 20 ml of 5 % dextrose solution) administered intravenously over 20 to 30 minutes may be preferred.

The patient's temperature, pulse, respiration, and blood pressure should be recorded every 30 minutes for 2 to 4 hours. (Note: See 'Intolerance Therapy' under **WARNINGS AND SPECIAL PRECAUTIONS**). A patient with severe rapidly progressing fungal infection, with good cardiopulmonary and renal function and who tolerates the test dose without a severe reaction, may then receive 0,3 mg/kg FUNGIZONE intravenously over a period of 2 to 6 hours. In patients with cardiac or renal impairment or a severe reaction to the test dose, therapy should be initiated with smaller daily doses (i.e. 5 to 10 mg). Doses may gradually be increased by 5 to 10 mg per day to a final daily dosage of 0,5 to 0,7 mg/kg. There are insufficient data presently available to define total dosage requirements and duration of treatment necessary for eradication of mycoses such as mucormycosis. The optimal dose is unknown. Total daily dosage may range up to 1,0 mg/kg per day, or up to 1,5 mg/kg on alternate days, in severe infections caused by less susceptible pathogens. Several months of therapy are usually necessary; a shorter period of therapy may produce an inadequate response and lead to relapse.

Caution

Under no circumstances should a total daily dosage of 1,5 mg/kg be exceeded. FUNGIZONE Intravenous overdoses can result in potentially fatal cardiac or cardio-respiratory arrest (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

The duration of treatment for deep-seated mycoses may be 6 to 12 weeks or longer.

Note: If symptoms of intolerance (See **SIDE-EFFECTS**) develop, they may be made less severe by additional therapy methods (See **WARNINGS AND SPECIAL PRECAUTIONS - Concomitant Medication: Intolerance Therapy**).

Rhinocerebral mucormycosis, a fulminating disease, generally occurs in association with diabetic ketoacidosis. It is imperative that rapid restoration of diabetic control be achieved in order for treatment with FUNGIZONE Intravenous to be successful.

Since rhinocerebral mucormycosis usually follows a rapidly fatal course, the therapeutic approach must necessarily be more aggressive than that used in more indolent mycoses and FUNGIZONE Intravenous therapy doses typically range from 0,7 to 1,5 mg/kg per day.

Reconstitution of solutions:

An initial concentrate of 5 mg amphotericin B per ml is first prepared by rapidly injecting 10 ml Sterile Water for Injection **without a bacteriostatic agent** directly into the lyophilised cake, using a sterile needle (minimum 20 gauge) and syringe. Shake the vial immediately until the colloidal solution is clear. The infusion solution is prepared by taking sufficient concentrate and diluting this with 5 % Dextrose Injection such that the final concentrate is 0,1 mg amphotericin B per ml. The pH of the Dextrose Injection should be ascertained before use and should be above 4,2.

Commercial Dextrose Injection usually has a pH above 4,2; however, if it is below 4,2, then 1 or 2 ml of buffer should be added to the Dextrose Injection before it is used to dilute the concentrated solution of amphotericin B. The recommended buffer has the following composition:

Dibasic sodium phosphate (anhydrous)	1,59 g
Monobasic sodium phosphate (anhydrous)	0,96 g
Water for Injection	qs 100,0 ml

The buffer should be sterilised before it is added to the Dextrose Injection, either by filtration through a bacterial retentive stone, mat, or membrane, or by autoclaving for 30 minutes at 103,4 kPa pressure (121 °C).

Caution

Aseptic technique must be observed strictly in the preparation of the buffer and infusion, since no preservative or bacteriostatic agent is present in the antifungal or in the materials used to prepare it for administration. All entries into the vial or into the diluents must be made with a sterile needle.

Do not reconstitute with saline solutions. The use of any diluent other than the ones recommended or the presence of a bacteriostatic agent (e.g. benzyl alcohol) in the diluent may cause precipitation of the antifungal.

Do not use the initial concentrate or the infusion solution if there is any evidence of precipitation or foreign matter in either one.

An in-line membrane filter may be used for intravenous infusion of amphotericin B; **however, the mean pore diameter of the filter should not be less than 1,0 micron in order to assure passage of the colloidal dispersion.**

SIDE EFFECTS:

The table below lists all adverse events for FUNGIZONE Intravenous and is presented by system organ class and frequency, which is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	**FREQUENCY**	**MedDRA Term**
Blood and Lymphatic System Disorders	Common	Anaemia
	Not known	Agranulocytosis, coagulopathy, eosinophilia, leukocytosis, leukopenia, thrombocytopenia
Immune System Disorders	Not known	Anaphylactoid/anaphylactic reactions
Nervous System Disorders	Not known	Convulsions, headache, encephalopathy, neurologic symptoms, neuropathy peripheral
Eye Disorders	Not known	Vision blurred, diplopia

Ear and Labyrinth Disorders	Not known	Deafness, tinnitus, vertigo
Cardiac Disorders	Not known	Arrhythmias, including ventricular fibrillation, cardiac arrest, cardiac failure
Gastrointestinal Disorders	Very common	Nausea, vomiting
	Not known	Dyspepsia, haemorrhagic gastroenteritis, upper abdominal pain, diarrhoea, melena
General Disorders and Administration Site Conditions	Very common	Chills, pyrexia [(b)]
	Uncommon	Flushing
	Not known	Pain, malaise, injection site pain with or without phlebitis or thrombophlebitis
Hepatobiliary Disorder	Common	Abnormal hepatic function
	Not known	Acute liver failure, jaundice
Investigations	Very common	Hypokalaemia [(a)], increased blood creatinine [(a)]
	Not known	Hyperkalemia, decreased weight
Metabolism and Nutrition Disorders	Common	Hypomagnesaemia
	Not known	Anorexia
Renal and Urinary Disorders	Very common	[(a)] Abnormal renal function test includes: uraemia, hyposthenuria, renal tubular acidosis, and nephrocalcinosis
	Not known	Hypocalcaemia
Respiratory, Thoracic and	Very common	Dyspnoea

Mediastinal Disorders	Not known	Allergic alveolitis, bronchospasm, non-cardiogenic pulmonary edema
Skin and Subcutaneous Tissue Disorders	Common	Rash
	Not known	Rash maculopapular, pruritus, skin exfoliation, toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and Connective Tissue Disorders	Not known	Arthralgia, myalgia
Vascular Disorders	Very common	Hypotension
	Not known	Hypertension, shock

[a] These usually improve with interruption of therapy. However, some permanent impairment often occurs, especially in those patients receiving large cumulative amounts (over 5 g) of amphotericin B. Concomitant diuretic therapy may increase the risk for renal impairment, whereas sodium repletion or supplementation may reduce the occurrence of nephrotoxicity (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

[b] Sometimes accompanied by shaking chills usually occurring 15 to 20 minutes after initiation of treatment.

Post-Marketing Adverse events:

The following post-marketing adverse events were reported:

Blood and Lymphatic system disorders: Agranulocytosis, coagulopathy, eosinophilia, leukocytosis, leukopenia, thrombocytopenia

Cardiac disorders: dysrhythmias, including ventricular fibrillation, cardiac arrest, cardiac failure

Ear and Labyrinth disorders: deafness, tinnitus and vertigo

Eye disorders: blurred vision, diplopia

Gastrointestinal disorders: upper abdominal pain, diarrhoea, melena

General disorders and administration site conditions: pain, malaise and injection site pain with or without phlebitis or thrombophlebitis

Hepatobiliary disorder: acute liver failure, jaundice

Immune system disorders: anaphylactoid/anaphylactic reactions

Investigations: hyperkalaemia

Metabolism and Nutrition disorders: weight decreased, anorexia

Musculoskeletal and Connective Tissue disorders: arthralgia, myalgia

Nervous system disorders: convulsions, headache, encephalopathy, neurologic symptoms, peripheral neuropathy

Renal and Urinary disorders: acute renal failure, anuria, nephrogenic diabetes insipidus, oliguria, renal impairment

Respiratory, Thoracic and Mediastinal disorders: bronchospasm, noncardiogenic pulmonary oedema

Skin and Subcutaneous Tissue disorders: maculopapular rash, pruritus, skin exfoliation, toxic epidermal necrolysis, Stevens-Johnson syndrome

Vascular disorders: hypertension and shock.

In addition, the following are post-marketing events observed in clinical trials:

Blood and Lymphatic system disorders: Anaemia

General disorders and administration site conditions: fever, chills

Investigations: hypokalaemia, increased serum creatinine

Metabolism and Nutrition disorders: hypomagnesaemia

Vascular disorders: hypotension

Renal and urinary disorders: renal function abnormalities

Hepatobiliary disorder: liver function test abnormalities

Gastrointestinal disorders: nausea and vomiting

Skin and Subcutaneous Tissue disorders: rash.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment of overdosage should be symptomatic and supportive. FUNGIZONE Intravenous overdoses can result in fatal cardiac or cardio-respiratory arrest. If an overdose is suspected, discontinue therapy and monitor the patient's clinical status (e.g. cardio-respiratory, renal and liver function, haematologic status, serum electrolytes) and administer supportive therapy as required. Amphotericin B is not haemodialysable. Prior to reinstituting therapy, the patient's condition should be stabilised (including correction of electrolyte deficiencies, etc.).

IDENTIFICATION:

Injection: Dry : A yellow to orange, fine fluffy powder, or a dry cake.

Reconstituted product : A collodial dispersion practically free from visible evidence of contamination.

PRESENTATION:

FUNGIZONE Intravenous is supplied in clear vials as a sterile lyophilised powder providing 50 mg amphotericin B and 41 mg sodium desoxycholate with 20,2 mg sodium phosphate as a buffer.

STORAGE INSTRUCTIONS:

FUNGIZONE Intravenous in powder form should be stored in the refrigerator, between 2 - 8 ° protected against exposure to light. The concentrate (i.e. 5 mg amphotericin B per ml after reconstitution of the powder with 10 ml Sterile Water for Injection) may be stored, protected against exposure to light, at room temperature for 24 hours, or at refrigerator temperatures for one week with minimal loss of potency and clarity. Any unused material should then be discarded. Solutions prepared for intravenous infusion (0,1 mg or less amphotericin B per ml) should be used promptly after preparation and should be protected from light during administration. Any unused concentrate should be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A/20.1.7/0150

NAME AND BUSINESS ADDRESS OF APPLICANT

Equity Pharmaceuticals (Pty) Ltd. *

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria, 0157

DATE OF PUBLICATION OF THIS PACKAGE INSERT

12 April 2019

*Authorised user of the ™ FUNGIZONE.