SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fungizone 50mg Powder for Sterile Concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains amphotericin B 50,000 units (50 mg).

Excipient with known effect:
Each vial contains approximately 2.68 mg of sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Concentrate for Solution for Infusion (Powder for Sterile Concentrate).

Fungizone powder is a fine yellow to orange fluffy powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fungizone should be administered primarily to patients with progressive, potentially fatal infections. This potent drug should not be used to treat the common forms of fungal disease which show only positive skin or serological tests.

Fungizone is specifically intended to treat cryptococcosis (torulosis); North American blastomycosis; the disseminated forms of candidosis, coccidioidomycosis and histoplasmosis; mucormycosis (phycomycosis) caused by species of the genera Mucor, Rhizopus, Absidia, Entomophthora, and Basidiobolus sporotrichosis (Sporotrichum schenckii), aspergillosis (Aspergillus fumigatus).

Amphotericin B may be helpful in the treatment of American mucocutaneous leishmaniasis but is not the drug of choice in primary therapy.

4.2 Posology and method of administration

Non-equivalence of amphotericin products

Different amphotericin products (sodium deoxycholate, liposomal, lipid complex) are not equivalent in terms of pharmacodynamics, pharmacokinetics and dosing and so the products should not be used interchangeably without accounting for these differences. Both the trade name, common name and dose should be verified pre-administration.

Under no circumstances should a total daily dose of 1.5 mg/kg be exceeded. Fungizone overdoses can result in potentially fatal cardiac or cardiorespiratory arrest (see section 4.4 & 4.9).

Posology

Fungizone should be administered by intravenous infusion over a period of 2-6 hours. Reduction of the infusion rate may reduce the incidence of side-effects. Initial daily dose should be 0.25 mg/kg of body weight gradually increasing to a level of 1.0 mg/kg of body weight depending on individual response and tolerance. Within the range of 0.25-1.0 mg/kg the daily dose should be maintained at the highest level which is not accompanied by unacceptable toxicity.

In seriously ill patients the daily dose may be gradually increased up to a total of 1.5 mg/kg. Since amphotericin B is excreted slowly, therapy may be given on alternate days in patients on the higher dosage schedule. Several months of therapy are usually necessary; a shorter period of therapy may produce an inadequate response and lead to relapse.

When commencing all new courses of treatment, it is advisable to administer a test dose immediately preceding the first dose. A volume of the infusion containing 1 mg (i.e. 10 mL) should be infused over 20-30 minutes and the patient carefully observed for at least a further 30 minutes. It should be noted that patient responses to the test dose may not be predictive of subsequent severe side effects.

Patients with a severe and rapidly progressing fungal infection, with good cardiopulmonary function and who tolerates the test dose without a severe reaction, may then receive 0.3 mg/kg amphotericin B intravenously over a period of 2 to 6 hours. For patients with cardiopulmonary impairment or severe reaction to the test dose, a lower dose (i.e. 5 to 10 mg) is recommended.

Doses may gradually be increased by 5 to 10 mg per day to a final daily dosage of 0.5 to 1 mg/kg.

Whenever medication is interrupted for a period longer than seven days, therapy should be resumed by starting with the lowest dosage level, i.e. 0.25 mg/kg of body weight and increased gradually.

The recommended concentration for intravenous infusion is 10 mg/100 mL.

Paediatric population

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 with reports of side effects similar to those seen in adults.

Older people

No specific dosage recommendations or precautions.

The use of Fungizone by other routes has been documented in the published literature:

Bladder irrigation/instillation (e.g. candiduria): Continuous irrigation with 50 mg Fungizone in 1 litre sterile water each day until urinary cultures are negative. Intermittent use of volumes of 100-400 mL (concentrations of 37.5-200 mcg/mL) has also been reported. The urine should be alkalinised (with potassium citrate) and antifungal ointment applied to the perineal area.

Lung inhalation (e.g. pulmonary aspergillosis): 8-40 mg amphotericin B (nebulised in sterile water or 5% Glucose) has been given daily in divided doses. Concurrent eradication of oral and intestinal yeast reservoirs is recommended.

Intrathecal (e.g. coccidiodal meningitis): Patients who do not respond to fluconazole or itraconazole would be candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment. The intrathecal dosage of amphotericin B normally ranges between 0.1 mg and 1.5 mg per dose, administered at intervals ranging from daily to weekly, beginning at a low dosage and increasing the dosage until the appearance of patient intolerance. Amphotericin B is irritating when injected into the CSF.

Other: Other uses of solutions prepared using Fungizone include local instillations for the treatment of fungal infections of the ear, eye, peritoneum, lung cavities and joint spaces.

Method of administration

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to such therapy , or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prolonged therapy with amphotericin B is usually necessary. Unpleasant reactions are quite common when the drug is given parenterally at therapeutic dosage levels. Some of these reactions are potentially dangerous. Hence amphotericin B should be used parenterally only in hospitalised patients, or those under close clinical observation.

Accidental overdose

Care must be taken when administering Fungizone to prevent overdose, which can result in potentially fatal cardiac or cardiorespiratory arrest. **Verify the product name and dosage pre-administration, especially if the dose prescribed exceeds 1.5 mg/kg** (see section 4.2 & 4.9).

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. Reduction of the infusion rate may reduce the incidence of side-effects (see section 4.2).

Infusion related reactions

While some patients may tolerate full intravenous doses of amphotericin B without difficulty, most will exhibit some intolerance particularly during the initiation of therapy. In patients experiencing adverse reactions these may be made less severe by giving aspirin, other antipyretics, antihistamines or anti-emetics. Pethidine (25 to 50 mg IV) has been used in some patients to decrease the duration or intensity of shaking chills and fever following amphotericin B therapy. Febrile reactions may be decreased by the intravenous administration of small doses of adrenal corticosteroids, e.g. 25 mg hydrocortisone.

This may be administered just prior to or during amphotericin B infusion. The dosage and duration of such corticosteroid therapy should be kept to a minimum. Administration of the drug on alternate days may decrease anorexia and phlebitis. Adding a small amount of heparin (1000 units per infusion) to the infusion, rotation of the injection site, the use of a paediatric scalp-vein needle and alternate day therapy may lessen the incidence of thrombophlebitis and coagulation problems. Extravasation may cause chemical irritation.

Corticosteroids should not be administered concomitantly unless they are necessary to control drug reactions.

Renal toxicity

Renal function test abnormalities are commonly observed and usually improve upon 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 be a predisposition for renal impairment, whereas sodium repletion or supplementation may reduce the occurrence of nephrotoxicity.

If serum creatinine exceeds 260 micromol/L the drug should be discontinued or the
dosage markedly reduced until renal function is improved. Weekly blood counts and
serum potassium determinations are also advisable. Low serum magnesium levels
have also been noted during treatment with amphotericin B.

Hepatic toxicity

Therapy should be discontinued if liver function test results (elevated bromsulphalein, alkaline phosphatase and bilirubin) are abnormal.

Neurotoxicity

Leucoencephalopathy has been reported very occasionally following the use of amphotericin B injection in patients who received total body irradiation. Most of these patients received high cumulative doses of amphotericin B.

Reports of neurological events such as arachnoiditis, myelopathy, paresis and paralysis have been associated with the intrathecal route of administration, see section 4.2 Intrathecal (e.g. coccidioidal meningitis).

Other nephrotoxic antibiotics and antineoplastic agents should not be given concomitantly except with great caution.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per Fungizone 50 mg vial, i.e. essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of nephrotoxic drugs or antineoplastics should be avoided if at all possible.

The hypokalaemia following amphotericin B therapy may potentiate the toxicity of digitalis glycosides or enhance the curariform actions of skeletal muscle relaxants.

Corticosteroids and Corticotrophin (ACTH) may increase the potassium loss due to amphotericin B.

Flucytosine toxicity may be enhanced during concomitant administration, possibly due to an increase in its cellular uptake and/or impairment of its renal excretion.

Acute pulmonary reactions have occasionally been observed in patients given amphotericin B during or shortly after leukocyte transfusions. It is advisable to separate these infusions as far as possible and to monitor pulmonary function.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Safety for use in pregnancy has not been established; therefore it should be used during pregnancy only if the possible benefits to be derived outweigh the potential risks involved.

Breastfeeding
It is not known whether amphotericin B is excreted in human milk. As excretion of amphotericin B in human milk is possible, and considering its potential toxicity, it should be used in nursing mothers only if the possible benefits to be derived outweigh the potential risks involved. In addition, it is prudent to advise a nursing mother to discontinue nursing.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The table below lists all adverse events. The list 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	Adverse Event (MedDRA)
Blood and Lymphatic System Disorders	Common	Anaemia
	Uncommon	Agranulocytosis, leukopenia, thrombocytopenia
	Rare	Coagulopathy*, eosinophilia, leucocytosis
Immune System Disorders	Rare	Anaphylactoid/anaphylactic reactions
Metabolism and Nutrition Disorders	Very common	Hypokalaemia
	Common	Hypomagnesemia, decreased appetite
	Rare	Hyperkalaemia*
Nervous System Disorders	Common	Headache
	Uncommon	Neuropathy peripheral
	Rare	Encephalopathy, convulsion
Eye Disorders	Rare	Vision blurred, Diplopia
Ear and Labyrinth Disorders	Rare	Deafness, tinnitus and vertigo
Cardiac Disorders	Uncommon	Arrhythmias including ventricular fibrillation*
	Rare	Cardiac arrest and cardiac failure*
Vascular Disorders	Very common	Hypotension
	Rare	Hypertension, shock
Respiratory, Thoracic and Mediastinal Disorders	Very common	Dyspnoea
	Uncommon	Bronchospasm
	Rare	Alveolitis allergic, non-cardiogenic pulmonary oedema
Gastrointestinal Disorders	Very common	Nausea, vomiting
	Common	Diarrheoa
	Uncommon	Abdominal pain upper
	Rare	Dyspepsia, hemorrhagic

		gastroenteritis, melaena
Hepatobiliary Disorders	Common Uncommon Rare	Liver function test abnormalities*, hepatic function abnormal Jaundice Acute hepatic failure
Skin and Subcutaneous Tissue Disorders	Common Rare	Rash Rash maculopapular, pruritus, skin exfoliation, toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and Connective Tissue Disorders	Uncommon Rare	Myalgia Arthralgia
Renal and Urinary Disorders	Very common Common Uncommon Rare	Renal function test abnormalities includes: azotemia, hyposthenuria, renal tubular acidosis and nephrocalcinosis (see section 4.4) Renal failure acute* Renal impairment* Anuria, nephrogenic diabetes insipidus, oliguria
General Disorders and Administration Site Conditions	Very common Common Uncommon Rare	Chills* (usually occurring within 15 to 20 minutes after initiation of treatment), pyrexia Injection site pain* (with or without phlebitis or thrombophlebitis) Flushing Pain & malaise
Investigations	Very common Rare	Blood creatinine increased* Weight decreased

* see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance

of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Amphotericin B overdoses can result in potentially 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.).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives for systemic use: ATC code: J02AA01

Amphotericin B is a polyene antifungal antibiotic active against a wide range of yeasts and yeast-like fungi including *Candida albicans*. Crystalline amphotericin B is insoluble in water; therefore, the antibiotic is solubilised by the addition of sodium desoxycholate to form a mixture which provides a colloidal dispersion for parenteral administration. 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 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 and fungal cells may share common mechanisms. No strains of Candida resistant to amphotericin B have been reported in clinical use, and although in vitro testing does produce a small number of resistant isolates this occurs only following repeated subcultures.

5.2 Pharmacokinetic properties

An initial intravenous infusion of 1 to 5 mg of amphotericin B per day, gradually increased to 0.65 mg/kg daily, produces peak plasma concentrations of approximately 2 to 4 mg/L which can persist between doses since the plasma half-life of amphotericin B is about 24 hours. It has been reported that amphotericin B is highly bound (more than 90%) to plasma proteins and is poorly dialysable.

Amphotericin B is excreted very slowly by the kidneys with 2 to 5% of a given dose being excreted in biologically active form. After treatment is discontinued the drug can be detected in the urine for at least seven weeks. The cumulative urinary output over a seven day period amounts to approximately 40% of the amount of drug infused.

Details of tissue distribution and possible metabolic pathways are not known.

5.3 Preclinical safety data

No further relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients: desoxycholic acid, concentrated phosphoric acid, sodium hydroxide, disodium phosphate dodecahydrate, monosodium phosphate dehydrate.

6.2 Incompatibilities

Do not reconstitute with saline solutions. The use of any diluent other than the ones recommended or the presence of a bacteriostatic agent in the diluent may cause precipitation of the amphotericin B

6.3 Shelf life

2 years

The concentrate (5 mg per ml after reconstitution with 10 mL sterile Water for Injections) should be stored protected from light. The absence of any antimicrobial preservative and the risk of contamination during reconstitution mean that the product should be stored for no more than 8 hours at room temperature (25°C) or 24 hours in a refrigerator (2-8°C). Should the need arise and a validated aseptic reconstitution technique is applied, the product is chemically stable when stored for 24 hours at room temperature or one week in a refrigerator. It is not intended as a multidose vial. Any unused material should be discarded. Solutions prepared for intravenous infusion (i.e. 10 mg or less amphotericin B per 100 mL) should be used promptly after preparation.

6.4 Special precautions for storage

Vials of powder for reconstitution should be stored in a refrigerator.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I flint glass vials closed with a grey chlorobutyl rubber stopper.
Vials of 50mg

6.6 Special precautions for disposal

Preparation of solutions:

Reconstitute as follows: An initial concentrate of 5 mg amphotericin B per ml is first prepared by rapidly expressing 10 mL sterile water for injection, without a bacteriostatic agent, directly into the lyophilised cake, using a sterile needle (minimum diameter: 20 gauge) and syringe. Shake the vial immediately until the colloidal solution is clear. The infusion solution, providing 10 mg/100 mL is obtained by further dilution (1:50) with 5% Glucose Injection of pH above 4.2. The pH of each container of Glucose Injection should be ascertained before use. Commercial Glucose 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 Glucose Injection before it is used to dilute a 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 Injections BP	q.s. to 100 mL

The buffer should be sterilised before it is added to the Glucose Injection, either by filtration through a bacterial filter, or by autoclaving for 30 mins at 15 lb pressure (121°C).

CAUTION:
Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present. Do not use the initial concentrate or the infusion solution if there is any evidence of precipitation of foreign matter.

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 amphotericin B dispersion.

Other preparations for injection should not be added to the infusion solution or administered via the cannula being used to administer Fungizone.
Aseptic technique must be strictly observed during the preparation of the concentrate, the buffer and the infusion.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Limited
8 The Chase, John Tate Road
Hertford
SG13 7NN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:01 September 1971
Date of latest renewal: 27 October 2010

10 DATE OF REVISION OF THE TEXT

14/10/2021