Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fungizone 50 mg Powder for sterile concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of amphotericin B.

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 yellow to orange, fine, 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, Conidiobolus* 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

Posology
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 1mg (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.

Fungizone should be administered by intravenous infusion over a period of 2-6 hours (in rare instances infusion times of up to 6 hours may be necessary). 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.
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.

CAUTION:

Under no circumstances should a total daily dose of 1.5 mg/kg be exceeded. Amphotericin B overdoses can result in potentially fatal cardiac or cardiorespiratory arrest. The recommended concentration for intravenous infusion is 10mg/100 mL.

Amphotericin B may be the only effective treatment available for potentially life-threatening fungal disease. In each case, its possible life-saving benefit must be balanced against its untoward and dangerous side effects.

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 without reports of unusual side effects.

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 alkalinized (with potassium citrate) and antifungal ointment applied to the perineal area.

Lung inhalation (e.g. pulmonary aspergillosis): 8-40 mg amphotericin B (nebulized 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 0.1mg and 1.5mg 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

To detect idiosyncratic anaphylactic reactions and to minimise the dose administered if such a reaction occurs, a test dose should be administered initially.
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. The drug is nephrotoxic. If the 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 and renal and hepatic function should also be monitored regularly during treatment. If any deterioration occurs in these parameters administration of the drug should cease immediately. Low serum magnesium levels have also been noted during treatment with amphotericin B. Therapy should be discontinued if liver function test results (elevated bromsulphalein, alkaline phosphatase and bilirubin) are abnormal.

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).

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.

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

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 sections 4.2 and 4.9).**

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 interactions

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

The hypokalaemia following amphotericin B therapy may potentiate the effects or toxicity of agents such as digitalis glycosides, anti-arrhythmic agents and skeletal muscle relaxants.

Corticosteroids and Corticotropin (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. It is recommended that women taking amphotericin B do not breast-feed because of the potential for serious adverse reactions in nursing infants.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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.

Addition of heparin (1000 units per infusion), rotation of the injection site, the use of a paediatric scalp-vein needle and alternate-day therapy may lessen the incidence of thrombophlebitis.
Extravasation may cause chemical irritation.

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, leukocytosis,
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
CardiacDisorders	Uncommon	Arrhythmias (including ventricular fibrillation)
	Rare	Cardiac arrest, 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	Diarrhoea
	Uncommon	Abdominal pain upper
	Rare	Dyspepsia, hemorrhagic gastroenteritis, melaena
Hepatobiliary Disorders	Common	Liver function test abnormal, hepatic function

	Uncommon Rare	abnormal Jaundice Acute hepaticfailure,
Skin and Subcutaneous TissueDisorders	Common Rare	Rash Rash maculopapular, pruritus, skin exfoliation, toxicepidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and Connective TissueDisorders	Uncommon Rare	Myalgia Arthralgia,
Renal and Urinary Disorders	Very common Common Uncommon Rare	Renal function test abnormal includes*:azotemia, hyposthenuria, renal tubular acidosis, and nephrocalcinosis, 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 sitepain (with or without phlebitis or thrombophlebitis) Flushing Pain, malaise
Investigations	Very common Rare	Blood creatinine increased Weight decreased

**This usually improves 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.*

The following adverse events have been seen with intrathecal administration: arachnoiditis, myelopathy, paresis and paralysis.

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie.

4.9 Overdose

Under no circumstances should a total daily dose of 1.5mg/kg be exceeded. The recommended concentration for IV infusion is 10mg/100mL. Amphotericin B overdoses can result in potentially fatal 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

Average peak plasma concentrations ranging from 0.5 to 2 mcg/mL are found in adults given repeated doses of approximately 0.5 mg/kg/day. Following a rapid initial fall, plasma concentrations plateau at about 0.5 mcg/mL. An elimination half-life of approximately 15 days follows an initial plasma half-life of 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.

Excretion in the bile may represent an important route of elimination. Details of other metabolic pathways are not known. Blood levels are not affected by renal or hepatic disease.

5.3 Preclinical safety data

No further relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Desoxycholic acid
Disodium phosphate dodecahydrate
Monosodium phosphate dihydrate
Sodium hydroxide
Concentrated Phosphoric acid

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

Unopened: 2 years
Reconstituted: After reconstitution with 10 mL sterile Water for Injections the concentrate (5 mg/mL) should be stored protected from light. Chemical and physical in-use stability has been demonstrated for 8 hours at up to 25°C and 24 hours at 2-8°C.

From a microbiological point of view, due to the absence of any microbial preservative, 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. These would normally not be longer than 24 hours at 2-8 °C unless reconstitution has taken place in controlled and validated aseptic conditions. 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 (2-8°C).

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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 lyophilized cake, using a sterile needle (minimum diameter: 20 gauge) and syringe. Shake the vial immediately until the colloidal solution is clear. The reconstituted product is a yellow solution. 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) 1.59g
Monobasic sodium phosphate (anhydrous) 0.96g
Water for Injections Ph.Eur. q.s. to 100mL

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

7 MARKETING AUTHORISATION HOLDER

Cheplapharm Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/004/001.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

April 2019
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