SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

AmBisome® (50 mg, intravenous infusion)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each vial contains 50 mg Amphotericin B (50 000 units) encapsulated in liposomes.

After reconstitution, the concentrate contains 4 mg/mL amphotericin B.

Excipient with known effect:

Contains sugar: Sucrose 900 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Yellow lyophilised cake or powder, free of visible evidence of contamination.

Reconstituted solution: Translucent, yellow emulsion, essentially free of visible contamination or agglomerates.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AmBisome is indicated for:

- empirical treatment of presumed fungal infection in febrile neutropaenic adults and children unresponsive to anti-bacterial treatment.
- the treatment of *severe systemic and/or deep mycoses* in adults and children in whom

toxicity (particularly nephrotoxicity) precludes the use of conventional systemic amphotericin B, or in patients who are resistant to conventional amphotericin B.
Fungal infections successfully treated with AmBisome include: disseminated candidiasis, aspergillosis, mucormycosis, chronic mycetoma and cryptococcal meningitis.

- *Cryptococcal meningitis* in HIV-infected patients.
- primary therapy of *visceral leishmaniasis* in immunocompetent adults and children and immunocompromised adults (e.g. HIV positive).

AmBisome should not be used to treat the common clinically unapparent forms of fungal disease which show only positive skin or serologic tests.

4.2 Posology and method of administration

Posology

AmBisome should be administered by intravenous infusion over a 30–60-minute period and the patient closely observed.
For doses greater than 5 mg/kg/day, intravenous infusion over a 2-hour period is recommended (*see section 4.4*).
The recommended concentration for intravenous infusion is 0,20 mg/ml to 2,00 mg/ml amphotericin B as AmBisome (*see section 6.6*).

Adults

Dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient.

Treatment of mycoses:

- For treatment of systemic mycotic infections, therapy is usually instituted at a daily dose of 3 to 5 mg/kg of body weight for a minimum of 14 days.

Mucormycosis:

For suspected or confirmed infection, initiate treatment with 5 to 10 mg/kg, administered daily. In patients with brain involvement or solid-organ transplant, dose at 10 mg/kg, administered daily. Avoid slow escalation of doses. The duration of therapy should be determined on an individual basis. Courses of up to 56 days are commonly used in clinical practice; longer durations of therapy may be required for deep seated infections or in cases of prolonged courses of chemotherapy or neutropenia.

Doses greater than 5 mg/kg and up to 10 mg/kg have been used in clinical trials and clinical practice. There are limited data on the safety and efficacy of AmBisome for the treatment of mucormycosis at these higher doses, therefore, a benefit:risk assessment should be made on an individual patient level to determine whether the potential benefits of treatment are considered to outweigh the known increased risk of toxicity at higher AmBisome doses (*see section 4.4)*.

Cryptococcal Meningitis:

Single agent therapy: Initiate treatment with 3 to 6 mg/kg/day AmBisome for 14 days.

High-dose induction therapy in HIV associated cryptococcal meningitis:

Administer a single dose of 10 mg/kg AmBisome on day 1, in combination with daily flucytosine 100 mg/kg and daily fluconazole 1200 mg, both administered for 14 days. After the 2-week induction period, patients should receive fluconazole 800 mg daily for 8 weeks and then at a dose of 200 mg daily thereafter at the treating doctor's discretion.

- *Visceral leishmaniasis:* a dose of 1,0 to 1,5 mg/kg/day for 21 days or alternatively a dose of 3,0 mg/kg/day for 10 days can be used for treatment of visceral leishmaniasis. In immunocompromised patients (e.g. HIV positive), a dose of 1,0 to 1,5 mg/kg/day for 21 days may be used. Because of the risk of relapse, maintenance therapy or reinduction therapy may be necessary.

- *Empirical therapy:* Initiate treatment with 3 mg/kg, administered daily for 10 to 14 days, or until resolution of neutropenia.

Special populations

Paediatric Population:

Systemic fungal infections and fever of unknown origin have been successfully treated with AmBisome in paediatric patients, without reports of unusual adverse events. AmBisome has been studied in paediatric patients aged one month to 18 years old. Dosage should be calculated on the same per kg body weight basis as for adults.

The safety and efficacy of AmBisome has not been established in infants under one month old.

Elderly Population:

No alteration in dose or frequency of dosing is required.

Renal Impairment:

AmBisome has been successfully administered to patients with pre-existing renal impairment at doses of 1-5 mg/kg/day in clinical trials and no adjustment in dose or frequency of administration was required (*see section 4.4)*.

Method of administration

- AmBisome should be administered by intravenous infusion over a 30-60-minute period and the patient closely observed. For doses greater than 5 mg/kg/day, intravenous infusion over a 2-hour period is recommended *(see section 4.4).*
- The recommended concentration for intravenous infusion is 0,20 mg/ml to 2,00 mg/ml amphotericin B as AmBisome (*see section 6.6 Special precautions for*

disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product).

- For instructions on reconstitution and dilution of the product before administration *(see section 6.6*).
- AmBisome is provided as a unit dose product. DO NOT STORE partially used vials for future patient use. Discard any unused portions (*see section 6.4*).

4.3 Contraindications

- AmBisome is contraindicated in patients who have shown hypersensitivity to any of its constituents unless, in the opinion of the doctor, the condition requiring treatment is life-threatening and amenable only to AmBisome therapy.

4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions

- Anaphylaxis and anaphylactoid reactions have been reported in association with AmBisome infusion.
- If a severe anaphylactic/ anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of AmBisome.

Infusion-related reactions

- Other severe infusion-related reactions can occur during administration of AmBisome (*see section 4.8*). Although infusion-related reactions are not usually serious, consideration of precautionary measures for the prevention or treatment of these reactions should be given to patients who receive AmBisome therapy.

- Slower infusion rates (over two hours) or routine doses of diphenhydramine, paracetamol, pethidine, and/or hydrocortisone have been reported as successful in their prevention or treatment.

Renal effects

- AmBisome has been shown to be substantially less toxic than conventional amphotericin B; particularly with respect to nephrotoxicity, however, adverse reactions, including renal adverse reactions, may still occur.
- In studies comparing AmBisome 3 mg/kg daily with higher doses (5, 6 or 10 mg/kg daily), it was found that the incidence rates of increased serum creatinine, hypokalaemia and hypomagnesaemia were notably higher in the high dose groups.
- Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium, as well as renal, hepatic and haematopoietic function should be performed. This is particularly important in patients receiving concomitant nephrotoxic medications (*see section 4.5*).
- Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of AmBisome administration.
- If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reductions, treatment interruption or discontinuation.

Pulmonary effects

- Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leukocyte transfusions.
- It is recommended these infusions are separated by as long a period as possible and pulmonary function should be monitored.

Renal Dialysis Patients

- Data suggest that no dose adjustment is required in patients undergoing haemodialysis or filtration procedures, however, AmBisome administration should be avoided during the procedure.

Patients with Diabetes Mellitus

- It should be noted that AmBisome contains approximately 900 mg of sucrose in each vial.

Excipients that may have an effect:

- Each vial contains 900 mg of sucrose. Sucrose is metabolised to glucose and fructose. The glucose increases blood glucose concentrations in diabetes mellitus.
- The additive effect of concomitantly administered products containing fructose (or sorbitol) and dietary intake of fructose (or sorbitol) should be taken into account.
- Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not use AmBisome.
- This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of Interaction

No specific interaction studies have been performed with AmBisome. However, the following agents are known to interact with amphotericin B and may interact with AmBisome.

Nephrotoxic medications:

- Concurrent administration of AmBisome with other nephrotoxic agents, for example cyclosporine, aminoglycosides and pentamidine, may enhance the potential for

medicine-induced renal toxicity. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, AmBisome has relatively less nephrotoxicity.

- Regular monitoring of renal function is recommended in patients receiving AmBisome with any nephrotoxic medications.

Corticosteroids, corticotrophin (ACTH) and diuretics:

- Concurrent use of corticosteroids, corticotrophin (ACTH) and diuretics (loop and thiazide) may potentiate hypokalaemia.

Digitalis glycosides:

- AmBisome-induced hypokalaemia may potentiate digitalis toxicity.

Skeletal muscle relaxants:

- AmBisome-induced hypokalaemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine)

Antifungals:

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

Antineoplastic agents:

- Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm and hypotension.
- Antineoplastic agents should be given concomitantly with caution.

Leucocyte transfusions:

- Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leukocyte transfusions.
- It is recommended that these infusions are separated by as long a period as possible and pulmonary function should be monitored.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

The safety of AmBisome in pregnant women has not been established.

AmBisome should only be used during pregnancy if the possible benefits to be derived outweigh the potential risks to the mother and foetus.

Systemic fungal infections have been successfully treated in pregnant women with conventional amphotericin B without obvious effect on the foetus, but the number of cases reported is insufficient to draw any conclusions on the safety of AmBisome in pregnancy.

Breastfeeding

Safety in lactation has not been established.

It is unknown whether AmBisome is excreted in human breast milk.

Breastfeeding during treatment with AmBisome is not recommended.

Fertility

No effect on fertility expected.

4.7 Effects on ability to drive and use machines

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

Some of the undesirable effects of AmBisome may impact the ability to drive and use machines.

AmBisome may cause headache and chest tightness or pain (*see section 4.8)* but may have minimal effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Summary of the safety profile

Fever and chills/rigors are the most frequent infusion-related reactions expected to occur during AmBisome administration. Less frequent infusion-related reactions may consist of one or more of the following symptoms: back pain, chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, and hypotension. These resolved rapidly on stopping the infusion and may not occur with every subsequent dose or when slower infusion rates (over 2 hours) are used. In addition, infusion-related reactions may also be prevented by the use of premedication. However, severe infusion-related reactions may necessitate the permanent discontinuation of AmBisome.

The following adverse reactions have occurred with AmBisome, based on clinical trial data and post-marketing experience. The frequency is based on analysis from pooled clinical trials of 688 AmBisome treated patients. The frequency of adverse reactions identified from post-marketing experience is not known.

Adverse reactions are listed below by body system organ class using MedDRA and are sorted by frequency. Frequencies are defined as:

Very common: (≥ 1/10)

Common: (≥ 1/100 to < 1/10)

Uncommon: (≥ 1/1 000 to < 1/100)

Very rare (< 1/10 000)

Not known (cannot be estimated from the available data)

Tabulated list of adverse reactions

Body System	Undesirable effect			
	Very common	**Common**	**Uncommon**	**Not known**
Blood and the lymphatic system disorders:			thrombocytopenia	anaemia
Immune system disorders:			anaphylactoid reaction	anaphylactic reactions, hypersensitivity
Metabolism and nutrition disorders:	hypokalaemia	hyponatraemia, hypocalcaemia, hypomagnesaemia, hyperglycaemia		
Nervous system disorders:		headache	convulsions	
Cardiac disorders:		tachycardia		cardiac arrest, dysrhythmia
Vascular disorders:		hypotension, vasodilatation, flushing		
Respiratory, thoracic and mediastinal disorders:		dyspnoea	bronchospasm	
Gastrointestinal disorders:	nausea, vomiting	diarrhoea, abdominal pain		
Hepato-biliary disorders:		liver function tests abnormal, hyperbilirubinaemia, alkaline phosphatase increased		
Skin and subcutaneous tissue disorders:		rash		angioedema
Musculoskeletal, connective tissue and bone disorders:		back pain		rhabdomyolysis (associated with hypokalaemia), musculoskeletal pain (described as arthralgia or bone pain)
Renal and urinary disorders:		increased creatinine, blood urea increased		renal failure, renal insufficiency

Body System	Undesirable effect			
	Very common	**Common**	**Uncommon**	**Not known**
General disorders and administrative site conditions:	rigors, pyrexia	chest pain	phlebitis	

Description of selected adverse reactions

Infusion related reactions

- Fever and chills/rigors are the most frequent infusion-related reactions expected to occur during AmBisome administration.
- Less frequent infusion-related reactions may consist of one or more of the following symptoms: chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, hypotension, and musculoskeletal pain (described as arthralgia, back pain, or bone pain). These resolve rapidly on stopping the infusion and may not occur with every subsequent dose or when slower infusion rates (over 2 hours) are used.
  In addition, infusion-related reactions may also be prevented by the use of premedication. however, severe infusion-related reactions may necessitate the permanent discontinuation of AmBisome *(see section 4.4).*
- In two double-blind, comparative studies, AmBisome treated patients experienced a significantly lower incidence of infusion-related reactions, as compared to patients treated with conventional amphotericin B or amphotericin B lipid complex.
- In pooled study data from randomised, controlled clinical trials comparing AmBisome with conventional amphotericin B therapy in greater than 1 000 patients, reported adverse reactions were considerably less severe and less frequent in AmBisome treated patients, as compared with conventional amphotericin B treated patients.
- A randomized phase III study assessed a single 10 mg/kg dose of AmBisome with a backbone of 14 days flucytosine and fluconazole, compared to the control group (1-

week conventional amphotericin B plus flucytosine followed by 1 week of fluconazole) in the treatment of HIV-associated cryptococcal meningitis. The AmBisome treated patients experienced fewer grade 3 or 4 adverse events compared to the control group. The safety profile observed in this patient population was consistent with the overall safety profile for AmBisome.

Renal effects

- Nephrotoxicity occurs to some degree with conventional amphotericin B in most patients receiving the medicine intravenously.
- In two, double-blind studies, the incidence of nephrotoxicity with AmBisome (as measured by serum creatinine increase greater than 2,0 times baseline measurement), is approximately half of that reported for conventional amphotericin B or amphotericin B lipid complex.

Interference with Phosphorus Chemistry Assays

- False elevations of serum phosphate may occur when samples from patients receiving AmBisome are analyzed using the PHOSm assay (e.g. used in Beckman Coulter analyzers including the Synchron LX20).
- This assay is intended for the quantitative determination of inorganic phosphorus in human serum, plasma or urine samples.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

The toxicity of AmBisome due to overdose has not been defined. If overdose should occur, cease administration immediately. Carefully monitor clinical status including renal and hepatic function, serum electrolytes and haematologic status. Haemodialysis or peritoneal dialysis does not appear to enhance the elimination of AmBisome.

Special populations (including paediatric population):

No additional information is available in special populations.

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.2 Antimicrobials: Fungicides

Pharmacotherapeutic group: Antimycotics for systemic use, antibiotics; ATC code: J02AA01

Pharmacodynamic effects:

Amphotericin B is a macrocyclic, polyene antifungal antibiotic produced *by Streptomyces nodosus.* Liposomes are closed, spherical vesicles formed from a variety of amphiphilic substances such as phospholipids. Phospholipids arrange themselves into membrane bilayers when exposed to aqueous solutions.

The lipophilic moiety of amphotericin allows the agent to be integrated into the lipid bilayer of the liposomes. Amphotericin B is fungistatic or fungicidal depending on the concentration attained in body fluids and the susceptibility of the fungus. The agent probably acts by binding to sterols in the fungal cell membrane, with a resulting change in membrane

permeability, allowing leakage of a variety of small molecules. Mammalian cell membranes also contain sterols, and it has been suggested that the damage to human cells and fungal cells caused by amphotericin B may share common mechanisms.

Microbiology:

Amphotericin B is active *in vitro* against many species of fungi. Most strains of *Histoplasma capsulatum, Coccidiodes immitis, Candida* spp*, Blastomyces dermatitides, Rhodotorula, Cryptococcus neoformans, Sporothrix schenkii, Mucor mucedo* and *Aspergillus fumigatus*, are inhibited by concentrations of amphotericin B ranging from 0,03 to 1,0 μg/ml *in vitro*. Amphotericin B has minimal or no effect on bacteria and viruses.

AmBisome has been shown to be effective in animal models of visceral leishmaniasis (caused by *Leishmania infantum* and *Leishmania donovani*). In mice infected with *Leishmania infantum* and treated with AmBisome 3 mg/kg for 3-7 doses, all dosage regimens of AmBisome cured mice more promptly than sodium stibogluconate, and no toxicity was seen. In mice infected with *Leishmania donovani*, AmBisome was >5 times more effective and > 25 times less toxic than amphotericin B.

Special populations:

Paediatric population

The pharmacodynamic profile of AmBisome in paediatric patients is consistent with that described in adult patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of AmBisome, based upon total plasma concentrations of amphotericin B, was determined in cancer patients with febrile neutropenia and bone marrow transplant patients who received 1-2 hour infusions of 1,0 to 7,5 mg/kg/day AmBisome for 3 to 20 days.

AmBisome has a significantly different pharmacokinetic profile from that reported in the literature for conventional presentations of amphotericin B, with higher amphotericin B plasma concentrations (C_{max}) and increased exposure (AUC_{0-24}) following administration of AmBisome than conventional amphotericin B.

Absorption:

After the first and last dose and at steady state the pharmacokinetic parameters of AmBisome (mean ± standard deviation) ranged from:

C_{max}:	7,3 μg/ml (± 3,8) to 83,7 μg/ml (± 43,0)
$T_{½}$:	6,3 hr (± 2,0) to 10,7 hr (± 6,4)
AUC_{0-24}:	27 μg.hr/ml (± 14) to 555 μg.hr/ml (± 311)
Clearance (Cl):	11 ml/hr/kg (± 6) to 51 ml/hr/kg (± 44)
Volume of distribution (Vss):	0,10 l/kg (± 0,07) to 0,44 l/kg (± 0,27)

Minimum and maximum pharmacokinetic values do not necessarily come from the lowest and highest doses, respectively.

Following administration of AmBisome steady state was reached quickly (generally within 4 days of dosing).

Distribution:

AmBisome pharmacokinetics following the first dose appear non-linear such that serum AmBisome concentrations are greater than proportional with increasing dose.

This non-proportional dose response is believed to be due to saturation of reticuloendothelial AmBisome clearance. There was no significant drug accumulation in the plasma following repeated administration of 1 to 7,5 mg/kg/day.

Volume of distribution on day 1 and at steady state suggests that there is extensive tissue distribution of AmBisome.

Elimination:

After repeated administration of AmBisome the terminal elimination half-life ($t_{½}\beta$) for AmBisome was approximately 7 hours.

The excretion of AmBisome has not been studied.

Metabolism:

The metabolic pathways of amphotericin B and AmBisome are not known. Due to the size of the liposomes there is no glomerular filtration and renal elimination of AmBisome, thus avoiding interaction of amphotericin B with the cells of the distal tubuli and reducing the potential for nephrotoxicity seen with conventional amphotericin B presentations.

Special populations:

Renal Impairment

The effect of renal impairment on the pharmacokinetics of AmBisome has not been formally studied. Data suggest that no dose adjustment is required in patients undergoing haemodialysis or filtration procedures, however, AmBisome administration should be avoided during the procedure.

5.3 Preclinical safety data

In repeat dose toxicity studies in dogs (1 month), rabbits (1 month) and rats (3 months) at doses equal to or, in some species, less than the clinical therapeutic doses of 1 to 3 mg/kg/day, the target organs for AmBisome toxicity were the liver and kidneys, both known target organs for amphotericin B toxicity.

AmBisome was found to be non-mutagenic in bacterial and mammalian systems.

Carcinogenicity studies have not been conducted with AmBisome.

No adverse effects on male or female reproductive function were noted in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cholesterol

Distearoylphosphatidylglycerol (sodium salt)

Alpha tocopherol

Disodium succinate hexahydrate

Contains sugar: Sucrose

pH adjusters: Sodium hydroxide, hydrochloric acid.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product.

AmBisome is incompatible with saline solutions and may not be mixed with other medicines or electrolytes.

6.3 Shelf life

Unopened Product:

AmBisome Liposomal Amphotericin B 50 mg powder for concentrate for dispersion for Infusion: 4 years.

Product once reconstituted with water for injections:

AmBisome is a single dose unpreserved sterile lyophilisate. Therefore, from a microbiological point of view, once reconstituted, the product must 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 2-8 °C, unless reconstitution and dilution has taken place under controlled and validated aseptic conditions.

Where reconstitution and dilution are conducted under controlled and validated aseptic conditions the following may be used in determining use periods.

Chemical and physical stability have been demonstrated for storage as follows:

Glass vials: 24 hours at 25 ± 2 °C exposed to ambient light.

Glass vials: up to 7 days at 2-8 °C

Polypropylene syringes: Up to 7 days at 2-8 °C.

Do not freeze.

Product once reconstituted with water for injections and further diluted in dextrose:

Chemical and physical stability have been demonstrated at the following storage conditions using dextrose infusion as the dilution medium in PVC or Polyolefin infusion bags.

Table 1: Stability of product once reconstituted with water for injections and further diluted in dextrose

Diluent	Dilution	Concentration of Amphotericin B mg/mL	Maximum Duration of Storage at 2-8 °C	Maximum Duration of Storage at 25±2 °C
5 % Dextrose	1 in 2	2,0	7 days	48 hours
	1 in 8	0,5	7 days	48 hours
	1 in 20	0,2	4 days	24 hours
10 % Dextrose	1 in 2	2,0	48 hours	72 hours
20 % Dextrose	1 in 2	2,0	48 hours	72 hours

6.4 Special precautions for storage

- Do not store above 25 °C.
- DO NOT STORE partially used vials for future patient use.

- For storage conditions of the reconstituted medicinal product, see section 6.3 Shelf life.
- Store in the original package.

6.5 Nature and contents of container

AmBisome is presented in 15 ml or 20 ml sterile, clear, colourless, Type I glass vials.
The closure consists of a butyl rubber stopper and aluminium ring seal fitted with removable plastic cap.
Single-dose vials are packed ten per carton with 10 sterile disposable 5 micron syringe filters included.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

- Any unused product or waste material should be disposed of in accordance with local requirements.
- For single use only.
- Discard any unused contents.

READ THIS ENTIRE SECTION CAREFULLY BEFORE BEGINNING RECONSTITUTION.
AmBisome is NOT interchangeable with other amphotericin products.
AmBisome must be reconstituted using Sterile Water for Injection (without a bacteriostatic agent) and diluted in Dextrose solution (5 %, 10 % or 20 %) for infusion only.

The use of any solution other than those recommended, or the presence of a bacteriostatic agent (e.g. benzyl alcohol) in the solution, may cause precipitation of AmBisome.

AmBisome is NOT compatible with saline and must not be reconstituted or diluted with saline or administered through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion. If this is not feasible, AmBisome should be administered through a separate line.

Do NOT mix AmBisome with other medicines or electrolytes.

Aseptic technique must be observed in all handling, since no preservative or bacteriostatic agent is present in AmBisome, or in the material specified for reconstitution and dilution.

Vials of AmBisome Containing 50 mg of Amphotericin B are Prepared as Follows:
If you need to reconstitute more than one vial, **complete the whole reconstitution and dispersion process for one vial** before adding the sterile water to the next vial.

1. Add 12 ml of Water for Injection to the AmBisome vial, to yield a preparation containing 4 mg/ml amphotericin B.
2. IMMEDIATELY after the addition of water, SHAKE THE VIALS VIGOROUSLY for 30 seconds to completely disperse the AmBisome. After reconstitution the concentrate is a translucent, yellow dispersion. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained. Do not use if there is evidence of precipitation of foreign matter.
3. Calculate the amount of reconstituted (4 mg/ml) AmBisome to be further diluted (see table below).
4. The infusion solution is obtained by dilution of the reconstituted AmBisome with between one (1) and nineteen (19) parts dextrose solution (5 %, 10 % or 20 %) for infusion by volume, to give a final concentration in the recommended range of 2,00 mg/ml to 0,20 mg/ml amphotericin B as AmBisome (see table below).

5. Withdraw the calculated volume of reconstituted AmBisome into a sterile syringe. Using the 5-micron filter provided, instill the AmBisome preparation into a sterile container with the correct amount of Dextrose solution (5 %, 10 % or 20 %) for infusion.

An in-line membrane filter may be used for intravenous infusion of AmBisome. However, the mean pore diameter of the filter should not be less than 1,0 micron.

Preparation of AmBisome for Infusion

An example is provided in the table below of the preparation of AmBisome dispersion for infusion at a dose of **3 mg/kg/day** in dextrose 5 % solution for infusion. Note that this table relates to doses of **3 mg/kg/day** only, however other doses than this may be prescribed for a patient. If a dose other than 3 mg/kg/day has been prescribed for a patient, then the appropriate calculations must be undertaken and the table cannot be used.

Table 2: Example of the preparation of AmBisome dispersion for infusion at a dose of 3 mg/kg/day in dextrose 5 % solution for infusion

Weight of patient (kg)	Number of vials required to prepare dose*	Amount of AmBisome required by the patient (to be withdrawn for further dilution) **(mg)**	Volume of reconstituted AmBisome to be withdrawn for further dilution **(ml)****	To make up a 0,2 mg/ml final concentration (1 in 20 dilution)		To make up a 2,0 mg/ml final concentration (1 in 2 dilution)	
				Volume of 5 % dextrose needed (ml)	Total volume (ml; AmBisome plus 5 % dextrose)	Volume of 5 % dextrose needed (ml)	Total volume (ml; AmBisome plus 5 % dextrose)
10	1	30	7,5	142,5	150	7,5	15
25	2	75	18,75	356,25	375	18,75	37,5
40	3	120	30	570	600	30	60
55	4	165	41,25	783,75	825	41,25	82,5
70	5	210	52,5	997,5	1050	52,5	105
85	6	255	63,75	1211,25	1275	63,75	127,5

* The full contents of a vial(s) may not be required to prepare a dose for a patient.

** Each vial of AmBisome (50 mg) is reconstituted with 12 ml Water for Injection to provide a concentration of 4 mg/ml Amphotericin B.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

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RSA

Tel: +27 11 483 0060

8 REGISTRATION NUMBER(S)

36/20.2.2/0453

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2012

10 DATE OF REVISION OF TEXT

20 May 2025