Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

AmBisome Liposomal Amphotericin B 50 mg Powder for Concentrate for Dispersion for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains as active ingredient 50 mg of amphotericin B (50,000 units) encapsulated in liposomes. After reconstitution, the concentrate contains 4mg/mL amphotericin B.

Excipients with known effect:
Each vial contains 213 mg of hydrogenated soy phosphatidylcholine and 900 mg of sucrose.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder for Concentrate for Dispersion for Infusion.

A sterile, yellow lyophilised cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AmBisome is indicated in adults and children aged 1 month to 18 years old:

- for the treatment of *systemic mycotic infections* due to organisms susceptible to this anti-infective, such as cryptococcosis, North American blastomycosis, disseminated candidiasis, coccidioidomycosis, aspergillosis, histoplasmosis, mucormycosis and in the treatment of some cases of American mucocutaneous leishmaniasis.
- for the treatment of *fever of unknown origin (FUO)* in neutropenic patients. In this context, FUO is defined as persisting fever, unresponsive to at least 96 hours of antibiotic treatment; it is highly indicative for a systemic fungal infection in this patient population. Before initiating AmBisome treatment, common viral, parasitic or mycobacterial infections should also be excluded as far as possible as causes for the observed FUO.
- as the primary therapy of *visceral leishmaniasis* in immunocompetent patients including both adults and children. In immunocompromised patients (e.g. HIV positive) AmBisome is also indicated as the primary therapy of visceral leishmaniasis.

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

4.2 Posology and method of administration

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

- For treatment of systemic mycotic infections, therapy is usually instituted at a daily dose of 1.0 mg/kg of body weight, and increased stepwise to 3.0 mg/kg, as required. A cumulative dose of 1.0 – 3.0 g of amphotericin B as AmBisome over 3-4 weeks has been typical. Mucormycosis: Initiate treatment with 5 mg/kg, administered daily. 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 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).

- For fever of unknown origin in neutropenic patients therapy should be initiated at 1.0 mg/kg/day; the dose may be raised to 3 mg/kg/day if indicated.

- 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.

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 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).

Hepatic Impairment
No data are available on which to make a dose recommendation for patients with hepatic impairment. See Warnings and Precautions for Use (See section 4.4).

Method of administration
A test dose (1 mg) should be infused slowly for up to 10 minutes and the patient carefully observed for 30 minutes afterwards.

AmBisome should be administered by intravenous infusion over a 30 – 60 minute period. For doses greater than 5mg/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 as AmBisome (see section 6.6).

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

4.3 Contraindications

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

AmBisome contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions
Anaphylaxis and anaphylactoid reactions have been reported in association with AmBisome infusion. To detect idiosyncratic anaphylactic reactions and minimise the dose administered if a reaction occurs, a test dose should be administered initially. 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 amphotericin B-containing products, including 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 2 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 3mg/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. 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 reduction, treatment interruption or discontinuation. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Most of them occurred in patients with renal impairment, and some cases after potassium supplementation in patients with previous hypokalaemia. Therefore, renal function and laboratory evaluation of potassium, should be measured before and during treatment. This is particularly important in patients with pre-existing renal disease, who have already experienced renal failure, or in patients receiving concomitant nephrotoxic medications (see section 4.5).

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 that infusions are separated by as long a period as possible and pulmonary function should be monitored.

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

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 rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Nephrotoxic medications: Concurrent administration of AmBisome with other nephrotoxic agents, (for example ciclosporin, aminoglycosides and pentamidine) may enhance the potential for drug-induced renal toxicity in some patients. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, AmBisome was associated with significantly less nephrotoxicity compared to amphotericin B.

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

Corticosteroids, corticotropin (ACTH) and diuretics: Concurrent use of corticosteroids, ACTH and diuretics (loop and thiazide) may potentiate hypokalaemia.

Digitalis glycosides: AmBisome induced hypokalaemia and 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.

Leukocyte 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 these infusions are separated by as long a period as possible and pulmonary function should be monitored.

4.6 Fertility, pregnancy and lactation

Fertility
Teratogenicity studies in both rats and rabbits concluded that AmBisome has no teratogenic potential in these species.

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.

Lactation
It is unknown whether AmBisome is excreted in human breast milk. A decision on whether to breastfeed while receiving AmBisome should take into account the potential risk to the child as well as the benefit of breast feeding for the child and the benefit of AmBisome therapy for the mother.

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 presented below may impact the ability to drive and use machines.

4.8 Undesirable effects

Summary of adverse reactions
The following adverse reactions have been attributed to 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)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Uncommon: thrombocytopenia
Not known: anaemia

Immune system disorders

Uncommon: anaphylactoid reaction
Not known: anaphylactic reactions, hypersensitivity

Metabolism and nutrition disorders

Very common: hypokalaemia
Common: hyponatraemia, hypocalcaemia, hypomagnesaemia, hyperglycaemia, hyperkalaemia

Nervous system disorders

Common: headache
Uncommon: convulsion

Cardiac disorders

Common: tachycardia
Not known: cardiac arrest, arrhythmia

Vascular disorders

Common: hypotension , vasodilatation, flushing

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea
Uncommon: bronchospasm

Gastrointestinal disorders

Very common: nausea, vomiting
Common: diarrhoea, abdominal pain

Hepatobiliary disorders

Common: liver function tests abnormal, hyperbilirubinaemia, alkaline phosphatase increased

Skin and subcutaneous disorders

Common: rash
Not known: angioneurotic oedema

Musculoskeletal and connective tissue disorders

Common: back pain
Not Known: rhabdomyolysis (associated with hypokalemia), musculoskeletal pain (described as arthralgia or bone pain)

Renal and urinary disorders

Common: increased creatinine, blood urea increased
Not known: renal failure, renal insufficiency

General disorders and administration site conditions

Very common: rigors, pyrexia

Common: chest pain
Uncommon: 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.

Renal effects
Nephrotoxicity occurs to some degree with conventional amphotericin B in most patients receiving the drug 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 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 national reporting system: 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

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

Special populations (including paediatric population):
No additional information is available in special populations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and 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 drug 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 drug is thought to act 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, the antifungal component of AmBisome, shows a high order of in vitro activity against many species of fungi. Most strains of *Histoplasma capsulatum*, *Coccidioides immitis, Candida spp., Blastomyces dermatitidis, Rhodotorula, Cryptococcus neoformans, Sporothrix schenkii, Mucor mucedo* and *Aspergillus fumigatus*, are inhibited by concentrations of amphotericin B ranging from 0.03 to 1.0 mcg/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 3mg/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.

Pediatric 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 hour infusions of 1.0 to 7.5mg/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 (Cmax) and increased exposure (AUC_{0-24}) following administration of AmBisome than conventional amphotericin B.
After the first and last dose 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)
T½:	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).

Absorption
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.

Distribution:
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. 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 cells of the distal tubuli and reducing the potential for nephrotoxicity seen with conventional amphotericin B presentations.

Other 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

Hydrogenated soy phosphatidylcholine
Cholesterol
Distearoylphosphatidylglycerol
Alpha tocopherol
Sucrose
Disodium succinate hexahydrate
Sodium hydroxide
Hydrochloric acid

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

6.3 Shelf life

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

Product once reconstituted with water for injections:
AmBisome is a single dose unpreserved sterile lyophile. 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
	1 in 2	2.0	7 days	48 hours
5 % Dextrose	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

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

6.5 Nature and contents of container

AmBisome is presented in 15 ml, 20ml or 30 ml sterile, Type I glass vials. The closure consists of a butyl rubber stopper and aluminium ring seal fitted with a removable plastic cap. Single-dose vials are packed in ten per carton with 10 filters.

Not all pack sizes may be marketed.

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

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 drugs 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 are Prepared as Follows:

1. Add 12 ml of Water for Injection to each AmBisome vial, to yield a preparation containing 4 mg/ml amphotericin**.**

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 2.00mg/ml to 0.20mg/ml amphotericin 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 **3mg/kg/day** in dextrose 5% solution for infusion. Note that this table relates to doses of **3mg/kg/day** only, however other doses than this may be prescribed for a patient. If a dose other than **3mg/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 **3mg/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) **(ml)**	Volume of reconstituted AmBisome to be withdrawn for further dilution **(ml)****	To make up a 0.2mg/ml final concentration (1 in 20 dilution)		To make up a 2.0mg/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 (50mg) is reconstituted with 12ml Water for Injection to provide a concentration of 4mg/ml Amphotercin B.

For single use only. Discard any unused contents.

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

7 MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Ida Business & Technology Park
Carrigtohill
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2322/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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