SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Part II

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

AmBisome Liposomal Amphotericin B 50mg 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.

For a 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 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.
- AmBisome is indicated 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.
- AmBisome is indicated 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

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).

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.

- 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 Patients
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 Patients
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).

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

4.3 Contraindications
AmBisome is contraindicated in those patients who have shown hypersensitivity to the active substance or to any of the excipients, unless, in the opinion of the physician,

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 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.

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.

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. 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 reduction, treatment interruption or discontinuation.

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.

In the Treatment of Diabetic Patients: It should be noted that AmBisome contains approximately 900 mg of sucrose in each vial.

In the Treatment of 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.

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

Pregnancy

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

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

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.

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.

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	($\geq$ 1/10)
Common	($\geq$ 1/100 to < 1/10)
Uncommon	($\geq$ 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,

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

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

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 (C_{max}) 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)
$T_{½}$:	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).
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.
After repeated administration of AmBisome the terminal elimination half-life ($t_{½ß}$) 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.

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 subchronic 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
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

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, 20 ml 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) **(mg)**	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 International Limited
Granta Park
Abington
Cambridge CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PA 0911/001/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 13th December 1990

Date of last renewal: 13th December 2005

10. DATE OF REVISION OF THE TEXT

December 2012

ANNEX III

LABELLING AND PACKAGE LEAFLET

LABELLLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 VIALS)

1. NAME OF THE MEDICINAL PRODUCT

AmBisome®

Liposomal Amphotericin B 50mg

Powder for Concentrate for Dispersion for Infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50mg of amphotericin B encapsulated in liposomes consisting of

3. LIST OF EXCIPIENTS

hydrogenated soy phosphatidylcholine
cholesterol
distearoylphosphatidylglycerol
and alpha-tocopherol
together with 900mg sucrose
disodiumsuccinate hexahydrate
sodium hydroxide and hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

10 Single dose vials, sterile

5. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR INTRAVENOUS INFUSION ONLY.
See package insert for reconstitution and administration.
This product is intended to be reconstituted with water for injection and diluted with a dextrose solution.
Follow directions exactly.
For use on one occasion only.
Discard any unused surplus.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

AmBisome is not interchangeable with other amphotericin products.

8. EXPIRY DATE

Expiry Date:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Product authorization holder:
Gilead Sciences International Ltd.,
Granta Park,
Abington,
Cambridge,
CB21 6GT
UK

Manufacturer:
Gilead Sciences Ltd.,
Carrigtohill, County Cork, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

P.A. 911/1/1

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

AmBisome®

Powder for Concentrate for Dispersion for Infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Liposomal Amphotericin B 50mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Single dose vial, sterile

5. METHOD AND ROUTE(S) OF ADMINISTRATION

FOR INTRAVENOUS INFUSION ONLY
See package insert for reconstitution and administration.
The product is intended to be reconstituted with water for injection and diluted with a dextrose solution.
Follow directions exactly.
For use on one occasion only.
Discard any unused surplus.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

AmBisome is not interchangeable with other amphotericin products

8. EXPIRY DATE

Expiry Date:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Product authorization holder:
Gilead Sciences International Ltd.,
Granta Park, Abington, Cambridge, CB21 6GT, UK

12. MARKETING AUTHORISATION NUMBER(S)

P.A. 911/1/1

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET

Package leaflet: information for the user

AmBisome®
Liposomal Amphotericin B 50 mg
Powder for Concentrate for dispersion for infusion

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. What AmBisome is and what it is used for

What AmBisome is
AmBisome is an antifungal antibiotic. The active ingredient in AmBisome is amphotericin B.

AmBisome is given as an infusion into a vein (a drip) by a doctor or nurse.

What AmBisome is used for

AmBisome has been studied in patients aged one month and above.

AmBisome is used to treat serious infections caused by fungi:

- **Fungal infections of one or more organs inside the body**

- **Suspected fungal infections** in patients who have a **raised temperature and a low white blood cell count called *neutropenia***.
  Before you are given AmBisome your doctor will check that your fever is not due to bacteria or viruses and will try and treat the infection with a course of antibiotics.

- **Visceral leishmaniasis**, a disease caused by a parasite.

AmBisome is not used to treat common fungal infections that are not serious, for example skin infections

2. Before you are given AmBisome

Before your first treatment
Before your first treatment your doctor may give you a small amount of AmBisome. They will then wait for approximately 30 minutes to see whether you have an allergic reaction, before continuing the infusion of the full dose.

Your doctor will not give you AmBisome:
- **If you are allergic** (hypersensitive) to amphotericin B or any other ingredients of this medicine (listed in section 6). However, if **your condition is life-threatening** you may be given AmBisome if your doctor believes that only AmBisome can help you.
- **If you have previously had a severe allergic reaction** (*anaphylactic* or *anaphylactoid*) to AmBisome. Symptoms of such immediate and life-threatening allergic reactions include: flushing, itching, sickness, swelling of the face, mouth, tongue and airways, often enough to cause difficulty breathing.

➔ **Tell your doctor** if any of these applies to you, **you must not be given AmBisome**

Your doctor will take special care with AmBisome:
- **If you have a severe allergic (*anaphylactic* or *anaphylactoid*) reaction.** If this happens your doctor will stop the infusion.
- **If you get other reactions related to the infusion**. If this happens, your doctor may slow down the infusion, so you receive AmBisome over a longer period of time (approximately 2 hours). Your doctor may also give you medicines to prevent or treat infusion-related reactions, such as diphenhydramine (an antihistamine), paracetamol, pethidine (for pain relief) and/or hydrocortisone (an anti-inflammatory medicine that works by reducing the response of your immune system).
- **If you are taking other medicines that may cause kidney damage**, s*ee* the section *Other medicines and Ambisome*. AmBisome may cause damage to the kidney. Your doctor or nurse will take regular blood samples to measure your *creatinine* (a chemical in the blood that reflects kidney function), and electrolyte levels (particularly potassium and magnesium) because both of these can be abnormal if you have changes in your kidney function. This is particularly important if you are taking other medicines that can affect the way your kidney functions. The blood samples will also be tested for changes in your liver, and your body's ability to produce new blood cells and platelets. **If blood tests show a change in kidney function,** or other important changes your doctor may give you a lower dose of AmBisome or stop treatment.
- **If blood tests show that your potassium levels are low**. If this happens, your doctor may prescribe a potassium supplement for you to take while you are treated with AmBisome.
- **If you are receiving or recently had a white blood cell transfusion**. Sudden and severe problems in the lungs can happen if you are given AmBisome infusion during or shortly after a white blood cell transfusion. Your doctor will recommend that the infusions are separated by as long a period as possible. This will reduce the risk of lung problems, and your lungs will be monitored.
- **If you have kidney failure and are having dialysis**. Your doctor may start AmBisome treatment after the procedure has ended.

- **If you have diabetes**. AmBisome contains approximately 900 mg of sucrose (sugar) in each vial. Tell your doctor if you have diabetes.

Other medicines and AmBisome

Tell your doctor if you are taking any other medicines, or have recently taken any. This includes medicines and herbal products you bought without a prescription.

Medicines that may cause kidney damage:

- **Medicines that suppress the immune system** (*immunosuppressants*), such as ciclosporin.
- **Certain antibiotics** called *aminoglycosides* (including gentamicin, neomycin and streptomycin).
- **Pentamidine** a medicine used to treat pneumonia in people with AIDS and leishmaniasis.

➔ **Tell your doctor if you are taking any of these medicines.** AmBisome may make any kidney damage caused by the medicine worse. If you are taking any of these medicines, your doctor or nurse will take regular blood samples to check your kidneys.

Medicines that may lower your potassium levels:

- **Corticosteroids**, anti-inflammation medicines that work by reducing the response of your immune system.
- **Corticotropin** (ACTH), used to control the amount of corticosteroid produced by your body. The body produces corticosteroid in response to stress.
- **Diuretics**, medicines that increase the amount of urine your body produces. This includes furosemide.
- **Digitalis glycosides**, medicines produced from the foxglove plant and used to treat heart failure. AmBisome may worsen the side effects of digitalis, such as heart rhythm changes.
- **Muscle relaxants** usually used during surgery, such as tubocurarine. AmBisome may increase the muscle relaxant effect.

➔ **Tell your doctor if you are taking any of these medicines** or have had recent surgery where these drugs may have been used.

Other medicines:

- **Antifungal medicines,** such as flucytosine. AmBisome may worsen the side effects of flucytosine. This includes changes in the body's ability to produce new blood cells. This may be seen in blood tests.
- **Certain cancer medicines,** such as methotrexate, doxorubicin, carmustine and cyclophosphamide. Taking this type of medicine with AmBisome may cause kidney damage, wheezing or trouble breathing and low blood pressure.
- **White blood cell transfusions**. Sudden and severe problems in the lungs can happen if you are given AmBisome infusion during or shortly after a white blood cell transfusion. Your doctor will recommend that the infusions are separated by as long a period as possible. This will reduce the risk of lung problems and your lungs will be monitored.

➔ **Tell your doctor if you are taking any of these medicines** or receiving such transfusions.

Pregnancy and breast-feeding

Tell your doctor before you are given AmBisome if you are pregnant, planning to become pregnant, or if you are breast-feeding. Your doctor will only prescribe

AmBisome if they think the benefits of treatment outweigh the risks to you and your unborn child or your baby.

Do not drive or use machinery
Some of the possible side effects of AmBisome could affect your ability to drive or use machines safely, See Section 4, *Possible side effects*.

AmBisome contains sugar
Tell your doctor if you have an intolerance to sucrose or other sugars

Tell your doctor if you have diabetes. AmBisome contains approximately 900 mg of sugar (sucrose) in each vial.

3. How AmBisome is used

AmBisome is always given to you by a doctor or nurse. It is given as an infusion into a vein (a drip).

AmBisome must not be given by any other method.

To prepare the infusion AmBisome must be dissolved in sterile water for injection and then diluted with a solution containing dextrose. AmBisome must not be mixed with saline (salt) solutions or with other drugs or electrolytes.

AmBisome is not interchangeable with other amphotericin products.

Before your first treatment
Before your first treatment your doctor may give you a small amount of AmBisome. They will then wait for approximately 30 minutes to see whether you have an allergic reaction, before continuing the infusion of the full dose.

Dosage for adults and the elderly
Your dose of AmBisome will depend on your body weight and your own particular needs.

- **Fungal infections of one or more organs of the body:**

Treatment is normally started at 1 mg per kg of body weight, every day over 3 to 4 weeks. Your doctor may decide to increase the amount you receive to as high as 3 mg per kg body weight.

- **Suspected fungal infections in patients with a raised temperature and neutropenia:**

Treatment is normally started at 1 mg per kg body weight, per day. Your doctor may decide to increase the amount you receive to as high as 3 mg per kg body weight.

- **Visceral leishmaniasis:**

The usual dose is 1 to 1.5 mg per kg body weight, per day for 21 days, or 3 mg per kg body weight for 10 days.

If you have a severely weakened immune system (for instance, if you are HIV positive), the dose is 1 to 1.5 mg per kg body weight for 21 days. Due to the risk of

re-infection, on-going treatment or a further course of treatment may be needed.

Dosage for children
AmBisome has been used to treat children. The dose of AmBisome for a child is calculated per kg of body weight in the same way as for adults.
AmBisome is not recommended in babies under 1 month old.

Dosage for patients with kidney problems
No change in dose or frequency of infusion is required. Your doctor or nurse will take regular blood samples to test for changes in kidney function during AmBisome treatment.

How long will the infusion take?
Normally the infusion will take 30 to 60 minutes. For doses greater than 5 mg per kg of body weight per day, the infusion could take up to 2 hours.

4. Possible side effects

Like all medicines, AmBisome can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have a severe allergic reaction, chest pain, develop an irregular heart beat or kidney problems (signs include tiredness and passing less urine). Severe allergic reaction side effects may include: skin rash, difficulty breathing, wheezing, chest tightness, swelling of the airways/tongue/face/hands or feet, loss of consciousness, confusion or dizziness, rapid or irregular heart beat, vomiting and nausea.

Side effects during the infusion
You may get side effects during the infusion:
- **Very common** (*may affect more than 1 in 10 people treated*): fever, chills, and shivering.
- **Less frequent infusion-related side effects include:** chest tightness, chest pain, breathlessness, difficulty breathing (possibly with wheezing), flushing, a faster heart rate than normal, low blood pressure and musculoskeletal pain (described as joint pain, back pain, or bone pain).

These side effects clear up quickly when the infusion is stopped. These reactions may not happen with future infusions of AmBisome or with a slower infusion (over 2 hours). Your doctor may give you other medicines to prevent infusion-related reactions, or to treat the symptoms if you do get them. If you have a severe infusion-related reaction, your doctor will stop the AmBisome infusion and you should not receive this treatment in the future.

Very common side effects
(*may affect more than 1 in 10 people treated*)
- Low blood potassium levels, leading to feeling tired, confused, having muscle weakness or cramps
- Feeling sick or being sick
- Fever, chills or shivering.

Common side effects
(*may affect up to 1 in 10 people treated*)
- Low magnesium, calcium or sodium blood levels, leading to feeling tired, confused, muscle weakness or cramps
- High blood sugar levels
- Headache
- A faster heart rate than normal
- Widening of the blood vessels, causing low blood pressure and flushing
- Breathlessness
- Diarrhoea
- Stomach pain
- Rash
- Chest pain
- Back pain
- Abnormal results for liver or kidney function showing up in blood tests or urine tests.

Uncommon side effects
(*may affect up to 1 in every 100 people treated*)
- Bleeding into the skin, unusual bruising and bleeding for a long time after injury
- Fits or seizures (*convulsions*)
- Difficulty breathing, possibly with wheezing
- Pain and swelling around the vein where AmBisome has been infused.

Other side effects
It is not yet clear how frequently these side effects occur:
- low red blood cell levels (*anaemia*), with symptoms of excessive tiredness, being out of breath after light activity, and a pale complexion
- Heart attacks
- Kidney failure
- Severe swelling of the skin around the lips, eyes or tongue
- Breakdown of muscle
- Bone pain and joint pain

Interference with Phosphorus blood test results.
This medicine may interfere with a particular blood test that measures levels of phosphorus (called the PHOSm assay). Please tell your doctor that you are receiving this medicine before such blood tests.

➔ If you notice any side effects that you are worried about, whether they are listed in this leaflet or not, **tell your doctor.**

5. How to store AmBisome

AmBisome is stored in the pharmacy.

Keep out of the reach and sight of children.

Do not use AmBisome after the expiry date which is stated on the label.

Do not store above 25 ^{o}C. Do not store partially used vials for future patient use.

AmBisome is a single dose, unpreserved, sterile, freeze-dried yellow powder to be dissolved in water for injection and diluted with a dextrose solution before infusion into a vein. From a microbiological point of view, the product should be used immediately once dissolved and diluted. If it is not used immediately, in-use storage times and conditions prior to use are the responsibility of the doctor or pharmacist and would normally not be longer than 24 hours at 2°C to 8°C unless reconstitution (dissolving the powder in water for injection) and dilution have taken place in controlled conditions to prevent microbial contamination.

Where reconstitution (dissolving the powder in water for injection) and dilution with dextrose solution are carried out under controlled conditions the storage time varies depending on the concentration of dextrose used and the storage temperature. Please refer to the Summary of Product Characteristics for further information.

Do not use AmBisome if there is any evidence of deterioration or foreign matter.

6. Further information

What AmBisome contains
The active ingredient of AmBisome is amphotericin B. Each vial contains 50 mg of amphotericin B enclosed inside liposomes (small fat particles). The other ingredients are: hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol, alpha tocopherol, sucrose (sugar), disodium succinate hexahydrate, sodium hydroxide and hydrochloric acid.

What AmBisome looks like and contents of the pack
AmBisome is a sterile, bright yellow Powder for Concentrate for Dispersion for infusion.

It is presented in a 15 ml, 20 ml or 30 ml glass vial.

Each vial contains 50 mg of the active ingredient amphotericin B.

The closure consists of a rubber stopper and an aluminium ring seal fitted with a removable plastic cap.

Each carton contains 10 vials and 10 filters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is:
Gilead Sciences International Limited
Granta Park
Abington
Cambridge CB21 6GT
United Kingdom

AmBisome is manufactured by:

Gilead Sciences Limited,
IDA Business & Technology Park,
Carrigtohill,
County Cork,
Ireland

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For any information about this medicine or for alternative formats of this leaflet for the visually impaired, please contact the local representative of the Marketing Authorisation Holder:

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