DATA SHEET

1. AMBISOME® (Liposomal Amphotericin B 50 mg) for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains the active substance amphotericin B.P. equivalent to 50 mg of amphotericin B encapsulated in the bilayer of liposomes.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

AmBisome is a sterile, lyophilised product for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

AmBisome is indicated for:

- Prophylaxis in liver transplant patients at risk of systemic Candida, Aspergillus and Cryptococcus infections, and for
- The treatment of systemic fungal infections caused by organisms susceptible to Amphotericin B (see section 5.1 Clinical efficacy and safety).

AmBisome is indicated for empirical treatment of presumed fungal infections in febrile neutropaenic patients whose fever has failed to respond to broad spectrum antibiotic treatment.

AmBisome is indicated for the treatment of visceral leishmaniasis. Clinical studies of efficacy in visceral leishmaniasis are limited to *Leishmania infantum*.

4.2 Dose and method of administration

Dose

The recommended concentration for intravenous infusion is 0.20 mg/mL to 2.00 mg/mL amphotericin as AmBisome. Dosage of amphotericin as AmBisome must be adjusted to the specific requirements of each patient.

1. For systemic mycoses, therapy is usually instituted at a daily dose of 1.0 mg/kg/day of body weight, and increased stepwise to 5.0 mg/kg/day, as required.

   A cumulative dose of 1.0 to 3.0 g of amphotericin B as AmBisome over three to four weeks is 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 Special Warnings and Precautions).

AmBisome therapy has been administrated for as long as three months, with a cumulative dose of 16.8 g of amphotericin as AmBisome without significant toxicity.

2. For prophylaxis against invasive fungal infections in liver transplant recipients, AmBisome may be administered at a daily dose of 1 mg/kg/day for five successive days following transplantation.

3. In HIV-associated disseminated cryptococcosis, a dose of 3 mg/kg/day for up to 42 days may be used. Because of the high frequency of relapses, chronic suppressive therapy with another agent may be necessary after completion of a treatment course with AmBisome.

4. In immunocompetent patients, 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) with visceral leishmaniasis, a dose of 1.0 to 1.5 mg/kg/day for 21 days may be used.

5. For empirical treatment of presumed fungal infection of febrile neutropaenic patients, AmBisome therapy should be initiated at a daily dose of 1-3 mg/kg. The daily dosage may be adjusted based on the clinical condition, as required.

Special populations

Elderly Patients: There have been no systematic studies in elderly patients.

Hepatic Patients: No data are available on which to make a dose recommendation for patients with hepatic impairment.

Paediatric population

Candida, Aspergillus and visceral leishmaniasis infections have been treated with AmBisome in a limited number of paediatric patients, without reports of unexpected adverse events. Paediatric patients have received AmBisome at doses comparable to those used in adults on a per kilogram body weight basis.

Method of administration

AmBisome should be administered by intravenous infusion over 30 to 60 minutes. For doses greater than 5 mg/kg, intravenous infusion over a 2 hour period is recommended (see section 4.8 Undesirable events).

Directions for Reconstitution and Dilution

AmBisome must be reconstituted using Water for Injection (without a bacteriostatic agent) and then further diluted using 5% Glucose Injection.

AmBisome infusions are prepared as follows:

1. Add 12 ml of Sterile Water for Injection to each AmBisome vial, to yield a preparation containing the equivalent of 4 mg/mL amphotericin B.

2. **IMMEDIATELY** after the addition of water, **SHAKE THE VIAL VIGOROUSLY** for at least 30 seconds to completely disperse the AmBisome. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained. Each vial should be reconstituted/diluted in sequence.

3. Calculate the amount of reconstituted (4 mg/mL) AmBisome to be further diluted.

4. The infusion, providing the equivalent from 2 to 0.2 mg amphotericin B per mL, is obtained by dilution with the appropriate amount of 5% Glucose Injection.

5. Withdraw the calculated volume of reconstituted AmBisome into a sterile syringe. Attach the 5-micron filter provided to the sterile syringe and instill the AmBisome preparation into a sterile container with the correct amount of 5% Glucose Injection. Visually inspect the infusion for particulate matter.

Use only Water for Injections to reconstitute the powder/cake. Use only 5% Glucose Injection to dilute the reconstituted product to the appropriate concentration 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**, as this may filter out the active ingredient.

Do not use material if there is any evidence of precipitation or foreign matter. Aseptic technique must be observed in all handling, since no preservative or bacteriostatic agent is present in AmBisome, or in the materials specified for reconstitution and dilution.

As AmBisome contains no bacteriostatic agent, from a microbiological point of view, the reconstituted/diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8° C (see section 6.4 Special precautions for storage).

4.3 Contraindications

AmBisome is contraindicated in those patients who have shown hypersensitivity to any of its constituents.

4.4 Special warnings and precautions for use

In studies in febrile neutropaenic patients AmBisome has been shown to be substantially less toxic than conventional amphotericin B, however**,** adverse reactions may still occur with AmBisome (see section 4.8 Undesirable effects). In particular, caution should be exercised when prolonged therapy is required. Laboratory evaluation of renal, hepatic and haematopoietic function should be performed regularly, and at least once weekly. In addition, serum electrolytes, particularly potassium and magnesium should also be regularly monitored**.** Particular attention should be paid to patients receiving concomitant therapy with nephrotoxic drugs. Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of AmBisome administration. Renal function should be closely monitored in these patients.

AmBisome may be nephrotoxic despite being tolerated significantly better than other amphotericin B products. If clinically significant reduction in renal function or worsening of other parameters occurs during AmBisome therapy, consideration should be given to dose reduction, treatment interruption or discontinuation.

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.

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. Severe infusion-related reactions can occur during administration of amphotericin B-containing products, including AmBisome. Although infusion-related reactions are not usually serious, consideration of measures for prevention or treatment of these reactions should be given to patients who receive AmBisome therapy.

DO NOT RECONSTITUTE THE LYOPHILISED POWDER/CAKE WITH SALINE OR ADD SALINE TO THE RECONSTITUTED CONCENTRATE, OR MIX WITH OTHER DRUGS.

Leucocyte transfusions
Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leucocyte transfusions. It is recommended these 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
The administration of AmBisome should commence ONLY when dialysis is completed. Levels of serum potassium and magnesium should be monitored regularly.

4.4 Interaction with other medicines and other forms of interaction

Formal studies of interactions between AmBisome and other drugs have not been conducted. Interactions between amphotericin B and other drugs have been reported, patients given concomitant drug therapy should be monitored closely. Conventional amphotericin has been reported to interact with the following drugs: antineoplastic agents (cisplatin and nitrogen mustards, see below), corticosteroids, corticotropin (ACTH), diuretics (e.g loop and thiazide), digitalis glycosides and skeletal muscle relaxants (tubocurarine, see below).

Antineoplastic agents such as cisplatin and the nitrogen mustard compounds may enhance the potential for renal toxicity, bronchospasm and hypotension in patients receiving amphotericin B; such concomitant therapy should be used with caution.

Amphotericin B can induce hypokalaemia which in turn may enhance the effects of non-depolarising skeletal muscle relaxants (tubocurarine) and digitalis glycosides. To date, there have not been reports of this enhancement attributed to amphotericin B; but such concomitant therapy should be used with caution.

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

Adequate clinical studies of the use of the combination of flucytosine with AmBisome have not been conducted. Whilst synergy between flucytosine and amphotericin has been reported, amphotericin B may enhance the toxicity of flucytosine by increasing its cellular uptake and impeding its renal excretion.

Concurrent administration of AmBisome with other nephrotoxic agents, for example cyclosporin, aminoglycosides and pentamidine may increase the risk of nephrotoxicity in some patients. Regular monitoring of renal function is recommended in patients receiving AmBisome with any nephrotoxic medications. However, a pivotal study in FUO (94-0-002) has demonstrated that patients receiving concomitant cyclosporin and/or aminoglycosides experienced significantly less nephrotoxicity when receiving AmBisome as compared to conventional amphotericin B (see section 4.8 Undesirable effects).

It should be noted that this finding is based upon a retrospective analysis of the data from this study. To date no other studies, either prospectively or retrospectively, have analysed the interaction between AmBisome and concomitantly administered cyclosporin and/or aminoglycosides. Also this reported difference was not observed in the paediatric population under the age of 13 years, possibly because of better

tolerance of the nephrotoxic effects of conventional amphotericin B in that population.

There have been reports of patients experiencing headache, malaise, hypotension and dizziness during concomitant therapy of AmBisome with dipyridamole, but the contribution of an interaction between the two drugs to the causation of these events is unclear.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B2. Safety for use of AmBisome in pregnant women has not been established. No reproductive toxicity studies have been conducted with AmBisome or conventional amphotericin. 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 have been small. Therefore, AmBisome should only be used during pregnancy if the possible benefits outweigh the potential risks.

Breast-feeding

It is not known whether AmBisome is excreted into breast milk. It is therefore recommended that breast-feeding be discontinued during treatment.

4.7 Effects on ability to drive and use machines

The effects of AmBisome on the ability to drive and/or use machines have not been investigated. Some of the undesirable effects of AmBisome presented in section 4.8 below may impact the ability to drive and use machines.

4.8 Undesirable effects

In general, patients should be monitored for any type of adverse event associated with the use of amphotericin B. In particular, caution should be exercised when prolonged therapy is required. Patients who have experienced acute toxicity with conventional amphotericin B generally did not experience acute toxicity when AmBisome was substituted.

Infusion Related Reactions
AmBisome is generally well tolerated. The most frequent infusion related reactions of AmBisome are fever, rigors and chills.

Less frequent infusion-related reactions may consist of one or more of the following symptoms: chest tightness or pain, dyspnea, 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. Back pain has been reported to be moderate to severe back pain, with or without chest tightness or pain. In some instances this was associated with tachycardia or hypotension.

Characteristically, a patient develops low back pain within a few minutes after the start of an infusion. The symptoms cease rapidly when the infusion is stopped. The back pain does not occur with every dose and it usually does not recur when the infusion rate is slowed.

The following is a listing by body system of all adverse reactions (causality of related, probably related or possibly related) and their incidences reported during nine clinical trials involving 834 patients. Adverse events with a causality of not related have not been included.

Body as a Whole

abdominal pain	1.0%
fever - can be severe	2.8%

Rigors and pyrexia have been very commonly reported (≥ 10%).

Chest pain has commonly been reported (≥ 1% and < 10%). The following have all been reported with an incidence less than 1%: allergic reaction, asthenia, burning sensation, death, face oedema, fungal infection, influenza like symptoms, injection site pain, leg pain, malaise and pain.

Cardiovascular System

Tachycardia and vasodilatation have been commonly reported (≥ 1% and < 10%). The following have all been reported with an incidence less than 1%: cardiac failure, extrasystoles, hypotension and thrombophlebitis. There are post-marketing reports of bradycardia, cardiac arrest and arrhythmia.

Digestive System

nausea	1.9%
vomiting	1.3%

Diarrhoea has been commonly reported (≥ 1% and < 10%). The following have all been reported with an incidence less than 1%: constipation, dyspepsia, hepatic enzymes increased, hepatic function abnormal, hepatitis cholestatic, hepatocellular damage, hepatomegaly, jaundice, pancreatitis (on occasions severe), pruritis ani and venoocclusive liver disease.

Normally, abnormalities in liver function tests do not progress with an increase in the cumulative dose of AmBisome. Liver transplant recipients can have a significantly higher alkaline phosphatase post-operatively with AmBisome prophylaxis.

Immune System Disorders

Anaphylactoid reactions have been uncommonly reported (≥ 0.1% to < 1%). Anaphylactic reactions and hypersensitivity have also been reported (incidence not known).

Haemic and Lymphatic System

The following have all been reported with an incidence less than 1%: anaemia, granulocytopaenia, leucopaenia, splenomegaly and thrombocytopaenia.

Musculoskeletal and Connective Tissue Disorders

Common: Back Pain

Not Known: Rhabdomyolysis (associated with hypokalaemia) has been reported, musculoskeletal pain (described as arthralgia or bone pain).

Metabolic and Nutritional Disorders

alkaline phosphatase increased	1.6%
hypokalaemia	5.2%

Abnormal liver function tests, hyponatraemia and hyperbilirubinaemia have been commonly reported (≥ 1% and < 10%). The following have all been reported with an incidence less than 1%: bilirubinaemia, serum urea increased, creatine phosphokinase increased, cyanosis, hyperglycaemia, hyperkalaemia, hypernatraemia, hyperuricaemia, hypoalbuminaemia, hypocalcaemia, hypomagnesaemia, LDH increased, serum creatinine increased, oedema legs, SGOT increased, SGPT increased, cramps legs and tendon disorder.

Nervous System

Flushing has been commonly reported (≥ 1% and < 10%). The following have all been reported with an incidence less than 1%: anxiety, coma, convulsions, depression, dizziness, dystonia, hypertension, neuropathy, neurosis, paraesthesia, sensory disturbance and tremor.

Respiratory System

Dyspnoea has been commonly reported (≥ 1% and <10 %). The following have all been reported with an incidence less than 1%: bronchospasm, coughing, dysphonia, epistaxis, hypoxia, pulmonary haemorrhage, respiratory disorder and respiratory insufficiency.

Skin and Appendages

rash, on occasions severe	2.0%

The following have all been reported with an incidence less than 1%: folliculitis, rash erythematous, rash follicular, rash maculopapular, sweating increased and urticaria acute. Angioneurotic oedema has also been reported (incidence not known).

Urogenital System

nephropathy toxic	1.1%

Increased creatinine and blood urea have been commonly reported (≥ 1% and < 10%). The following have all been reported with an incidence less than 1%: albuminuria, nephrosis, renal abscess, renal failure acute, renal function abnormal and uraemia. Renal insufficiency and renal failure have also been reported (incidence not known).

Interference with Phosphorus Chemistry Assay:

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.

In Studies in Patients with Febrile Neutropaenia unresponsive to broad spectrum antibiotic therapy, the Adverse Event Response is represented by Table's 1 – 4 below:

Table 1. Most Common Adverse Events in any of the Treatment Groups (Incidence >20%) Study 94-0-002

	AmBisome (N=343)	**amphotericin B (N=344)**
Fever	307 (89.5%)	313 (91.0%)
Chills	163 (47.5%)*	261 (75.9%)
Hypokalaemia	147 (42.9%)*	174 (50.6%)
Nausea	136 (39.7%)	133 (38.7%)
Vomiting	109 (31.8%)	151 (43.9%)
Diarrhoea	104 (30.3%)	94 (27.3%)
Rash	85 (24.8%)	84 (24.4%)
Dyspnoea	79 (23.0%)	100 (29.1%)
Hyperglycaemia	79 (23.0%)	96 (27.9%)
Increased creatinine	77 (22.4%)*	145 (42.2%)
Increased alkaline phosphatase	76 (22.2%)	66 (19.2%)
Increased BUN	72 (21.0%)*	107 (31.1%)
Hypomagnesaemia	70 (20.4%)	88 (25.6%)
Abdominal pain	68 (19.8%)	75 (21.8%)
Headache	68 (19.8%)	72 (20.9%)
Hypocalcaemia	63 (18.4%)	72 (20.9%)
Increased cough	61 (17.8%)	75 (21.8%)
Epistaxis	51 (14.9%)	69 (20.1%)
Hypotension	49 (14.3%)	74 (21.5%)
Tachycardia	46 (13.4%)	72 (20.9%)

*A significantly lower incidence of chills, hypokalaemia, increased creatinine and increased BUN was observed for patients administered AmBisome compared with those administered amphotericin B, *$p<0.05$, Chi-square.

Table 2. Incidence of Severe (Grade 3 or Grade 4 Toxicity) Experienced in either Treatment Arm by at Least 5% of Patients - Study 94-0-002 and Study 97-0-034

	Study 94-0-002		Study 97-0-034		
	AmBisome 3 mg/kg/day (N=343)	amphotericin B 0.6 mg/kg/day (N=344)	AmBisome 3 mg/kg/day (N=85)	AmBisome 5 mg/kg/day (N=81)	Abelcet 5 mg/kg/day (N=78)
Total number (%) with any severe toxicity	198 (57.7%)***	272 (79.1%)	42 (49.4%)***	32 (39.5%)***	61 (78.2%)
Chills	35 (10.2%)***	147 (42.7%)	6 (7.1%)***	9 (11.1%)*	25 (32.1%)
Fever	24 (7.0%)***	70 (20.3%)	10 (11.8%)***	6 (7.4%)***	29 (37.2%)
Hyperglycaemia	26 (7.6%)	31 (9.0%)	---	---	---
Bilirubinaemia	25 (7.3%)	29 (8.4%)	5 (5.9%)	0	1 (1.3%)
Dyspnea	20 (5.8%)*	37 (10.8%)	4 (4.7%)	2 (2.5%)	6 (7.7%)
Diarrhoea	17 (5.0%)	12 (3.5%)	---	---	---
Respiratory failure	17 (5.0%)	14 (4.1%)	3 (3.5%)	1 (1.2%)	4 (5.1%)
Hypokalaemia	---	---	3 (3.5%)	2 (2.5%)	8 (10.3%)
Hypotension	16 (4.7%)	20 (5.8%)	2 (2.4%)	1 (1.2%)	6 (7.7%)
Nausea	12 (3.5%)*	25 (7.3%)	0	2 (2.5%)	3 (3.8%)
Vomiting	4 (1.2%)**	19 (5.5%)	1 (1.2%)	3 (3.7%)	3 (3.8%)
Sepsis	---	---	2 (2.4%)	3 (3.7%)	5 (6.4%)
Creatinine Increased	---	---	2 (2.4%)	0	4 (5.1%)
Lung Disorder	---	---	2 (2.4%)	0	4 (5.1%)
Hypoxia	---	---	1 (1.2%)	1 (1.2%)	5 (6.4%)
Acute kidney failure	---	---	2 (2.4%)	1 (1.2%)	6 (7.7%)

Significantly lower incidence in the AmBisome group compared with the control group, p<0.001***, <0.01**, <0.05*, Chi-sq

Table 3. Changes in Serum Creatinine on Treatment as Compared to Baseline Values and Hypokalaemia on Treatment According to Cyclosporine Exposure in Study 94-0-002

	AmBisome		Amphotericin B	
	With Cyclosporine (N=42)	Without Cyclosporine (N=301)	With Cyclosporine (N=38)	Without Cyclosporine (N=306)
Nephrotoxicity (>1.5 x Baseline Serum Creatinine)				
- All	25 (60%)*	76 (25%)	34 (89%)	136 (44%)
- Paediatrics	4/6 (67%)	12/32 (38%)	2/3 (67%)	14/34 (41%)
- Adults	21/36 (58%)	64/269 (24%)	32/35 (91%)	122/172 (45%)
Hypokalaemia (<3 mmol/L)				
- All	8 (19%)	83 (28%)	5 (13%)	111 (36%)
- Paediatrics	3/6 (50%)	11/32 (34%)	0/3 (0%)	16/34 (47%)
- Adults	5/36 (14%)	72/269 (27%)	5/35 (14%)	95/272 (35%)

* p=0.0026 - versus amphotericin B group receiving cyclosporine

Table 4. Changes in Serum Creatinine on Treatment Compared to Baseline Values and Hypokalaemia on Treatment According to Aminoglycoside Exposure in Study 94-0-002

	AmBisome		Amphotericin B	
	With Aminoglycosides (N=227)	**Without Aminoglycosides (N=116)**	**With Aminoglycosides (N=227)**	**Without Aminoglycosides (N=117)**
Nephrotoxicity (>1.5 x Baseline Serum Creatinine)				
- All	74 (33%)*	27 (23%)	112 (49%)	58 (50%)
- Paediatrics	14/25 (56%)	2/13 (15%)	12/20 (60%)	4/17 (24%)
- Adults	60/202 (30%)	25/103 (24%)	100/207 (48%)	54/100 (54%)
Hypokalaemia (<3 mmol/L)				
- All	65 (29%)	26 (22%)	87 (38%)	29 (25%)
- Paediatrics	10/25 (40%)	4/13 (31%)	10/20 (50%)	6/17 (35%)
- Adults	55/202 (27%)	22/103 (21%)	77/207 (37%)	23/100 (23%)

*p=0.0001 versus amphotericin B group receiving aminoglycosides

4.9 Overdose

Symptoms
There have been no reports of patients who have been given overdoses of AmBisome. The symptoms of overdosage are likely to be an extension of the adverse reactions to AmBisome.
Management
If overdosage should occur, cease administration immediately. Symptomatic supportive measures should be instituted. Carefully monitor clinical status including renal and hepatic function, serum electrolytes and haematologic status. Haemodialysis or peritoneal dialysis does not appear to affect the elimination of AmBisome.

For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Amphotericin is a mixture of antifungal polyenes produced by the growth of *Streptomyces nodosus*. The major component of amphotericin, amphotericin B, is fungistatic or fungicidal depending on the drug concentration attained in body fluids and the susceptibility of the fungus. Its mechanism of action is partly due to its binding to a sterol (ergosterol) present in the membrane of sensitive fungi. This results in a change in membrane permeability allowing leakage of cell components. Mammalian cell membranes also contain sterols such as cholesterol to which amphotericin B has less binding affinity than to ergosterol. It has been suggested that

damage to human cells and fungal cells caused by amphotericin B may share common mechanisms.

AmBisome contains liposomal amphotericin. Liposomes are closed, spherical vesicles formed when certain polar lipids, such as phospholipids and cholesterol, are dispersed in water. Phospholipids arrange themselves into single or multiple concentric bilayer membranes when exposed to and homogenised in aqueous solutions. AmBisome contains single bilayer liposomes with the drug held in the membrane as a charge complex with distearoylphosphatidylglycerol. The liposomes are less than 100 nm in diameter.

AmBisome can remain intact in the circulation for prolonged periods and distributes as intact liposomes to tissues where fungal infections may occur. Both AmBisome and liposomes with the same lipid composition preferentially associate with the outer surface of fungal cell walls. AmBisome acts by liposome binding to the outer wall of fungi followed by drug release. On release the drug is thought to transfer to the ergosterol-rich fungal cell membrane for which it has high affinity. Interaction with fungi occurs both within and outside macrophages and is believed to be enzymatically mediated.

Microbiology

Amphotericin, 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 dermatitides*, Rhodotorula, *Cryptococcus neoformans*, *Sporothrix schenkii*, *Mucor mucedo* and *Aspergillus fumigatus*, are inhibited by concentrations of amphotericin ranging from 0.03 to 1.0 mcg/mL in vitro. Amphotericin has minimal or no effect on bacteria and viruses.

Clinical efficacy and safety

Treatment of Candida, Aspergillus and Cryptococcus Systemic Infections

AmBisome was studied in an open uncontrolled compassionate use study in patients with systemic fungal infections for whom no effective alternative therapy was available. Patient recruitment involved 138 infectious episodes in 128 patients: 79 males; 49 females. The mean age was 38.5 years (range 4 to 87). The mean weight was 61.00 kg (range 16.5 to 87.0). Hospitalised patients with evidence of severe or life-threatening invasive systemic fungal infection were enrolled for the following reasons:

1. prior amphotericin B toxicity (50 cases)
2. failure of previous antifungal therapy (37 cases)
3. renal insufficiency (34 cases)
4. other reasons (7 cases)
5. no reason stated (10 cases).

AmBisome was given as an intravenous infusion of 0.5 g/L in 5% dextrose over 30-60 minutes. The following initial doses were used:

1. Patients with history of amphotericin B nephrotoxicity:
    a. Start at 0.2 mg/kg/day below previous daily dose of amphotericin B.

2. Patients with failure to respond to amphotericin B alone or in combination:
    a. AmBisome dose same as previous amphotericin B dose.

3. Renal insufficiency not related to amphotericin B:
    a. 0.25 mg/kg/day initially.

In all cases, the AmBisome dose could be increased by 0.2 mg/kg/day to 3.0 mg/kg/day or higher with approval of the sponsor.

Duration of treatment: Range: 1 to 97 days.

Three categories of patients were treated:

1. Definitive diagnosis of systemic infection

Positive culture or microscopic identification of a fungus from tissue or blood where the fungus or colonisation/contamination were not normally found.

There were 60 definite fungal infections in 58 patients. One patient had two forms of pulmonary disease (aspergillosis pneumonia and aspergilloma). One patient had two different fungal infections (*Trichosporon capitatum* and *Aspergillus fumigatus*).

2. Presumptive systemic infection

a) Patients with positive serology and consistent clinical evidence (7 infections in 7 patients).
b) Patients with positive Candida cultures of bronchial lavage, with consistent clinical evidence (14 infections in 14 patients).
c) Patients with presumptive diagnosis only (clinical evidence only) (10 cases from 9 patients).

One patient had two separate presumptive fungal infections.

3. Refractory superficial infections

Definitive diagnosis restricted to superficial tissues, which failed to respond to available therapies (8 cases in 8 patients).

Patients were excluded from the efficacy analysis if:

(a) less than 8 days therapy was administered (26 cases)
(b) sufficient data was not available (13 cases).

Clinical and mycological efficacy was evaluated 48 hours after completion of AmBisome therapy.

Definitive Group

Clinical cure occurred in 19 (79%) of Candida cases, 7 (27%) of 26 Aspergillus cases, 6 (86%) of 7 Cryptococcus meningitis patients with AIDS.

In 56 mycologically evaluable cases, eradication occurred in 19 (83%) of 23 Candida cases, 9 (37.5%) of 24 Aspergillus cases, 5 (71.4%) of 7 patients with Cryptococcus meningitis with AIDS.

Presumptive Group
Clinical cure occurred in 12 of 22 cases with presumed Candida infection. There were 3 improvements, 5 failures and 2 non-evaluable cases. Cure occurred in 2 of 5 Aspergillosis cases, 2 cases improved and one was not evaluable.

Thirteen cases were mycologically evaluable - all Candida cases. Eradication occurred in 9 cases; persistence in 4 cases.

Superficial Group
There were 8 cases. Four Candida infections and one case of pulmonary Aspergillosis were cured.

Mycological evaluation was possible in only 3 cases. Two cases of Candida were eradicated.

Of the 138 episodes of fungal infection, the reason for enrollment was prior amphotericin B toxicity (50 cases) or renal insufficiency (34 cases). Among cases treated with AmBisome for greater or equal to 8 days enrolled with prior amphotericin B toxicity, 21/37 (57%) cases had a clinical cure as well as mycological eradication. For cases enrolled with renal insufficiency and treated for greater than or equal to 8 days, 13/21 (62%) cases had clinical cure and mycological eradication. Among the 13 cases enrolled with prior amphotericin B toxicity who were not evaluable, the reason for receiving less than 8 days of AmBisome therapy were: death unrelated to study drug (5 cases), investigator decision (2 cases), resolution of infection (2 cases) and one case each of patient request, intercurrent illness, an adverse event, and other reasons. For the 13 cases enrolled with renal insufficiency who received less than 8 days of AmBisome therapy, the reasons for study drug discontinuation were: death unrelated to study drug (9 cases), resolution of infection (2 cases), investigator decision (1 case) and unknown (1 case).

AmBisome may be safe and effective therapy for some patients with systemic fungal infections who have pre-existing renal insufficiency or have experienced prior amphotericin B toxicity.

Prophylaxis in Liver Transplant Patients

AmBisome was evaluated in a randomised placebo-controlled double-blind study as prophylaxis of fungal infections in liver transplant patients. The study compared 5 days therapy with either AmBisome (1 mg/kg/day) or placebo as prophylaxis against fungal infections in patients undergoing liver transplantation.

Proven infection - positive blood cultures from sterile body sites or deep organ biopsy during life. In addition, for Aspergillus species, preliminary x-ray findings and positive culture or microscopy in bronchoscopic lavage fluid or bronchoscopic biopsy. At autopsy - positive culture or microscopy from deep organ tissue.

Suspected infection - clinically ill patients without positive serological or fungal antigen findings.

For analysis of efficacy or prophylaxis, patients must have completed the full five day course of treatment. Cut off for analysis was 30 days post-transplantation.

There were 23 males in the placebo group and 15 males in the AmBisome group. All received orthotopic liver grafts. There was a larger proportion of placebo patients (27/37) with fungal colonisation prior to treatment than AmBisome patients (20/40). In other respects, patient characteristics did not differ between the groups. There was no difference between groups in a number of risk factors.

Eight of the 85 patients were not evaluated for efficacy (3 AmBisome; 5 placebo). The sole significant difference in outcomes was in proven fungal infections. There were six proven fungal infections in the placebo group (16%) (5 *Candida spp*; one *Aspergillus niger*), and none with the AmBisome treated group (0%) during the 30 day assessment period ($p<0.01$). Onset was 12 ± 5 (mean ± SE) days - range 6-20 days. Suspected fungal infections occurred in two AmBisome patients and no placebo patients. In both cases, suspicion was based on positive Cand-Tech test (day 11 and day 15, respectively).

Visceral Leishmaniasis

AmBisome was studied in three small open multicentre trials for treatment of visceral leishmaniasis. *Leishmania infantum* was the organism most commonly isolated as all patients were infected in Italy or nearby islands. Initially, two dose regimens were studied in immunocompetent patients. In the first study, 10 patients (4 adults; 6 children), including four with a history of relapse after previous alternative treatments, were given 1.0 to 1.5 mg/kg/day for 21 days. Clearance of parasites from splenic or bone marrow aspirates on microscopy was documented in 8/8 patients tested and from culture of the aspirate in 6/6 patients. Fever was present in 9/10 prior to treatment and eradicated from 10 patients.

In light of these results, a second group of immunocompetent patients (9 children, one adult) were treated with AmBisome 3 mg/kg/day for 10 days. Clearance from aspirate on microscopy occurred in 10/10 patients following therapy and from 3/3 aspirate cultures performed. Relapses in immunocompetent patients were not documented, but follow-up may have been incomplete.

The third study was performed in eleven immunocompromised subjects: 8 HIV-positive patients and 3 HIV-negative patients using a dose of 1.0 to 1.5 mg/kg/day for 21 days. Of the 8 HIV patients, all had clinical and parasitological eradication, but there was relapse in 3 of 8 within follow-up periods of up to 5 months. The eighth patient died of AIDS-related cerebral toxoplasmosis at 2 months. Among the 3 HIV-negative patients, one died during treatment (not AmBisome related) and one relapsed at 5 months.

Febrile Neutropaenic Patients Unresponsive to Broad Spectrum Antibiotic Agents.

AmBisome was studied in four randomised, comparator trials in neutropaenic patients unresponsive to broad-spectrum antibiotic therapy for at least three days including:

- One double-blind trial (94-0-002) comparing 343 AmBisome treated patients to 344 amphotericin B treated patients. AmBisome was dosed at 3 mg/kg daily and amphotericin B at 0.6 mg/kg daily. The doses could be increased by 50% or 100% or decreased by 50%, or interrupted, based on clinical response or toxicity.
- One double-blind trial (97-0-034) comparing AmBisome 3 mg/kg daily or 5 mg/kg daily to amphotericin B lipid complex (ABLC) 5 mg/kg daily in 85, 81, and 78 patients, respectively.
- Two open-label dose-finding trials evaluating AmBisome at 1 mg/kg or 3 mg/kg, or amphotericin B at 1 mg/kg daily. Trial 104-10 enrolled 134 adults and trial 104-14 enrolled 205 children with FUO. Patients in each study were equally distributed among the treatment arms.

Treatment was continued until resolution of fever for three days in the open-label trials, and until neutrophil recovering in the two double-blind trials. Mean treatment duration ranged from 7-16 days.

In the two double-blind trials, the definition of clinical success included: survival for 7 days post study drug; resolution of fever during neutropaenia; resolution of microbiologically confirmed baseline fungal infection, if applicable; no emergent fungal infection; no premature discontinuation of study drug due to toxicity or lack of efficacy. In the two open-labeled trials, clinical success was defined as: afebrile for ≥3 days until study end; no emergent fungal infection; no concomitant antifungal therapy.

In the Study 94-0-002 clinical success, based on a composite endpoint in a modified intent to treat analysis, was reported in 50.1% in the AmBisome 3 mg/kg group and 49.4% in the amphotericin B group. The 95% CI of the difference in overall success rates were –6.8% and +8.2%. Clinical success in each of the studies is presented in Table 5 below.

Table 5. Clinical success from Studies 94-0-002, 97-0-034, 104-10, and 104-14

Study	AmBisome 1mg/kg/day n(%)	AmBisome 3mg/kg/day n(%)	AmBisome 5mg/kg/day n(%)	Amphotericin B 0.6mg/kg/day n(%)	Amphotericin B 1mg/kg/day n(%)	ABLC 5mg/kg/day n(%)
94-0-002	-	171 (50%)	-	169 (49%)	-	-
97-0-034	-	34 (40%)	34 (42%)	-	-	26 (33%)
104-10	21 (45%)	29 (63%)	-	-	22 (55%)	-
104-14*	45 (64%)	45 (63%)	-	-	36 (53%)	-

*Children only

In Study 94-0-002, there were significantly more emergent proven infections in conventional amphotericin B treated patients compared to AmBisome treated patients (7.8% vs. 3.2%, respectively, p=0.009).

Overall in Study 94-0-002, AmBisome and conventional amphotericin B showed equivalent efficacy by the primary composite endpoint success.

Likewise, in Study 97-0-034 there were no statistically significant differences between AmBisome and amphotericin B lipid complex (ABLC) in terms of overall success rate. However, this trial was not adequately powered to enable a conclusion to be drawn about the efficacy equivalence of AmBisome and ABLC.

5.2 Pharmacokinetics properties

Pharmacokinetic data from animal studies demonstrated that higher peak plasma levels and greater total area under the curve values for amphotericin B were achieved after AmBisome administration, as compared to conventional intravenous amphotericin B. Higher levels of amphotericin were achieved in hepatic and splenic tissues with AmBisome in biodistribution studies in mice and rats. However, in rats amphotericin levels in renal tissue were 5 to 6 fold lower for a given dose of AmBisome, compared to conventional drug after repeated administration for 28 days. For other organs, tissue levels of amphotericin were similar, following dosing with AmBisome or with the conventional drug.

Absorption

AmBisome has a pharmacokinetic profile significantly different from that of conventional amphotericin B. In Phase I pharmacokinetic studies in patients a dose dependent increase in peak serum concentrations was observed between daily doses of 2 mg/kg to 5 mg/kg. The peak serum concentrations achieved with AmBisome are 6 to 10-fold greater than those reported for the conventional formulation. A dose-dependency was observed for AmBisome serum trough levels obtained 24 hours post-dosing. The apparent volume of distribution ranged from 18.9 L to 49.1 L, with mean values of 29.5 L, 28.6 L and 24.1 L for daily doses of 3, 4, and 5 mg/kg, respectively. Conventional amphotericin B has an apparent volume of distribution of 280 L and so the volume of distribution of AmBisome is approximately 1 to 18% that of amphotericin B.

Distribution

Detailed human tissue distribution and possible metabolic pathways of conventional amphotericin are not fully understood and have not been established for AmBisome.

Elimination

In all the pharmacokinetic studies, the total body clearance of AmBisome ranged from 0.5 to 1.3 L/hr. The total body clearance for amphotericin B is approximately 1.8 L/hr. In a single patient who received both conventional amphotericin B and AmBisome at equivalent doses, the area under the serum concentration curve (AUC) increased 13-fold for AmBisome relative to the conventional drug. Amphotericin B tissue concentrations were determined in autopsy material from three patients. Drug concentrations following AmBisome were highest in the liver and spleen, confirming data obtained from animal studies. Concentrations in the lungs, kidneys, brain, and heart were comparatively low.

Table 6 shows the results of a study in patients with AmBisome at doses of 3.0, 4.0, and 5.0 mg/kg/day. Some variability of the data in patients has been observed.

Table 6. Results of a study in patients with AmBisome at doses of 3.0, 4.0, and 5.0 mg/kg/day

	3.0 mg/kg	4.0 mg/kg	5.0 mg/kg
Maximum concentration (mcg/mL)	21.4	25.6	35.9
AUC (mcg•h/mL)	211	419	523
Clearance (L/h)	0.90	0.53	0.53
Volume of distribution (L)	29.5	28.6	24.1
Distribution half-life (h)	0.40	0.62	0.83
Elimination half-life (h)	26.0	38.2	32.4

These values were determined by pooling serial measurements of serum data at each dose level, generating a curve fit and calculating the pharmacokinetic parameters from that curve. Patient numbers were small and the number of measurements pooled was not constant across all patients at each dose level.

5.3 Preclinical safety data

No long term studies in animals have been performed to evaluate the carcinogenic potential of AmBisome or of conventional amphotericin B. There have been no studies to evaluate genotoxicity or whether fertility in males or females is affected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amphotericin B is encapsulated in the bilayer of liposomes consisting:

- Approximately 213 mg hydrogenated soy phosphatidylcholine
- 52 mg cholesterol
- 84 mg distearoylphosphatidylglycerol (as the sodium salt)
- 0.64 mg alpha-tocopherol
- 900 mg sucrose
- 27 mg sodium succinate hexahydrate.

6.2 Incompatibilities

DO NOT RECONSTITUTE THE LYOPHILISED POWDER/CAKE WITH SALINE OR ADD SALINE TO THE RECONSTITUTED CONCENTRATE, OR MIX WITH OTHER DRUGS.

AmBisome is not physically compatible with saline solutions and should not be mixed with other drugs or electrolytes. An existing intravenous line must be flushed with 5% Glucose Injection prior to infusion of AmBisome. If this is not feasible, AmBisome should be administered through a separate line.

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.

6.3 Shelf life

Unopened vials: 48 months

Reconstituted vials: 24 hours

6.4 Special precautions for storage

Unopened vials: lyophilised material should be stored below 25°C.

Reconstituted vials: should be stored at 2° to 8°C (Refrigerate, do not freeze)

DO NOT STORE partially used vial for future patient use.

AmBisome contains no bacteriostatic agent, from a microbiological point of view, the reconstituted/diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8° C. Infusions should be completed within this 24 hour timeframe. AmBisome is provided as a unit dose product. Product is for one dose in one patient only, discard any remaining contents.

6.5 Nature and Contents of Container

AmBisome is presented in single use vials and supplied in ten pack bulk cartons. Each carton presentation includes the directions for use and 5 micron filter(s) for use during dilution. Each vial contains amphotericin B.P. equivalent to 50 mg of amphotericin B.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Gilead Sciences (NZ)
C/- Grant Thornton New Zealand Limited,
L4, 152 Fanshawe Street
Auckland 1010
New Zealand

Tel: 0800 443 933

9. DATE OF FIRST APPROVAL

2 April 1998

10. DATE OF REVISION OF THE TEXT

21 December 2017

Summary table of changes

Section changed	Summary of new information
All	Data Sheet reformatted according to Data Sheet Explanatory Guide v1.0 March 2017
4.2	Dosage information for mucormycosis added
8	Change to Sponsor address

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