PRODUCT MONOGRAPH

[Pr]AmBisome®

liposomal amphotericin B for injection

50 mg Amphotericin B per vial

Antifungal

Distributed by:
Astellas Pharma Canada, Inc.
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PRODUCT MONOGRAPH

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THERAPEUTIC CLASSIFICATION

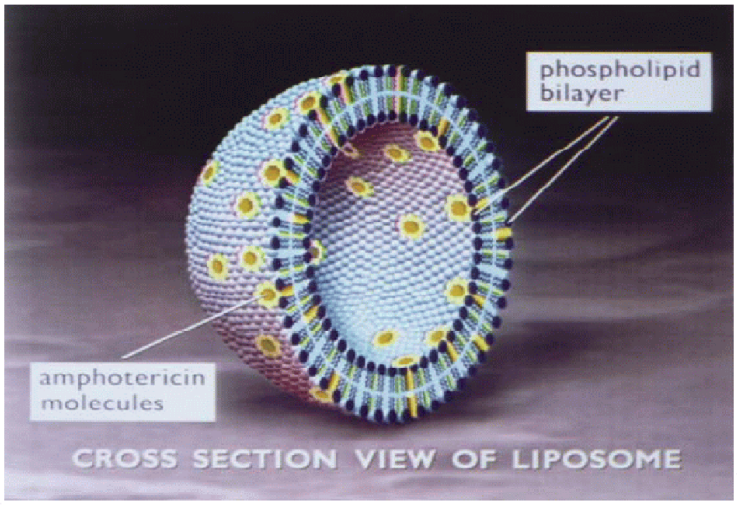
Antifungal

ACTION AND CLINICAL PHARMACOLOGY

The active component of AmBisome® (liposomal amphotericin B for injection) is amphotericin B, which acts by binding to the ergosterol component in the cell membrane of susceptible fungi. This results in a change in membrane permeability allowing leakage of cell components. While amphotericin B has a higher affinity for the ergosterol component of the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell membrane and the damage to human cells and fungal cells may share a common mechanism.

AmBisome is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphiphilic substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. AmBisome consists of these unilamellar bilayer liposomes with amphotericin B intercalated within the membrane, forming a charge transfer complex with the distearoyl phosphatidylglycerol. Due to the nature and quantity of amphiphilic substances used, and the lipophilic moiety in the amphotericin B molecule, the drug is an integral part of the overall structure of the AmBisome liposomes. AmBisome contains true liposomes that are less than 100 nm in diameter. The unique size of the AmBisome liposomes results in therapeutic levels at diverse sites of fungal infections within the body. A schematic depiction of the liposome is presented in Figure 1.

Figure 1: Schematic cross-section of a liposome with amphotericin B intercalated within its membrane.



Studies have shown that AmBisome can remain as an intact liposome and stay in circulation for prolonged periods of time. It is taken up and retained in tissues rich in reticuloendothelial cells where fungal infection may occur. Preclinical studies have shown that liposomes with and without amphotericin B bind to the fungal cell wall. AmBisome acts by liposomal binding to the outer cell wall of fungi followed by drug release. On release, the drug is thought to transfer to the ergosterol-rich fungal cell wall for which it has high affinity. Interaction with fungi occurs both within and outside macrophages. Liposomal and various lipid-complexed amphotericin B preparations differ significantly, in their pharmacokinetic profile and tissue distribution.

Pharmacokinetics

The pharmacokinetic profile of amphotericin B after administration of AmBisome is different from that of conventional amphotericin B (amphotericin B desoxycholate). In Phase I pharmacokinetic studies, AmBisome produced higher peak serum concentrations between daily doses of 1 mg/kg/day to 5.0 mg/kg/day (6 to 10-fold greater) and area under the serum concentration curve (AUC, approximately 13-fold higher) than those reported for conventional amphotericin B. The apparent volume of distribution ranged from 18.9 L to 49.1 L. The total body clearance of AmBisome ranged from 0.5 to 1.3 L/hr. Data are shown in Table 1. Detailed comparative studies with conventional amphotericin B are lacking. Some variability of the data in patients has been observed.

Amphotericin B concentrations were measured in autopsy material from three patients who died within 24 hours of receiving their last dose of AmBisome. Drug concentrations were highest in the liver and spleen (tissues rich in reticuloendothelial cells) confirming data obtained from animal studies. Concentrations in lungs, kidneys, brain and heart were comparatively low. Detailed human tissue distribution has not been established for AmBisome (see Pharmacology: Human Pharmacokinetics).

Table 1: Pharmacokinetic Parameters of AmBisome

Dose	1 mg/kg/day		2.5 mg/kg/day		5 mg/kg/day	
Day	**1 n=8**	**Last n=7**	**1 n=7**	**Last n=7**	**1 n=12**	**Last n=9**
PARAMETERS						
C_{max} (µg/mL)	7.3 ± 3.8	12.2 ± 4.9	17.2 ± 7.1	31.4 ± 17.8	57.6 ± 21.0	83.0 ± 35.2
AUC_{0-24} (µg•hr/mL)	27 ± 14	60 ± 20	65 ± 33	197 ± 183	269 ± 96	555 ± 311
$t_{1/2}$ (hr)	10.7 ± 6.4	7.0 ± 2.1	8.1 ± 2.3	6.3 ± 2.0	6.4 ± 2.1	6.8 ± 2.1
V (L/kg)	0.58 ± 0.40	0.16 ± 0.04	0.69 ± 0.85	0.18 ± 0.13	0.22 ± 0.17	0.11 ± 0.08
Vss (L/kg)	0.44 ± 0.27	0.14 ± 0.05	0.40 ± 0.37	0.16 ± 0.09	0.16 ± 0.10	0.10 ± 0.07
Cl (mL/hr/kg)	39 ± 22	17 ± 6	51 ± 44	22 ± 15	21 ± 14	11 ± 6

INDICATIONS AND CLINICAL USE

AmBisome (liposomal amphotericin B for injection) is indicated for empirical therapy for presumed fungal infection in febrile, neutropenic patients and for treatment of cryptococcal meningitis in HIV-infected patients. AmBisome is also indicated for the treatment of systemic or disseminated infections due to *Candida, Aspergillus* or *Cryptococcus* in patients who are refractory to or intolerant to conventional amphotericin B therapy or renally impaired patients.

In a randomized, double-blind study of 687 febrile, neutropenic patients treated with either AmBisome or conventional amphotericin B following at least 96 hours of broad spectrum antibiotic therapy, overall

therapeutic success rates for AmBisome and conventional amphotericin B were equivalent (49.9% vs 49.1%, respectively; see Pharmacology, Clinical Studies). In a randomized, double-blind study of 267 HIV-positive patients with cryptococcal meningitis, treated with either AmBisome or conventional amphotericin B, mycological success rates at week 2 for AmBisome and conventional amphotericin B were equivalent (53% vs 48%, respectively; see Pharmacology, Clinical Studies).

AmBisome was used in a compassionate study of 133 patients who had failed conventional amphotericin B therapy or who had nephrotoxicity from previous therapy or who had renal insufficiency. The overall mycological eradication rate was 62% (33/53 patients) and the overall clinical success rate was 82% (75/91 patients). Patients who entered this trial with high creatinine values due to nephrotoxicity returned to or toward normal values during AmBisome therapy.

CONTRAINDICATIONS

AmBisome (liposomal amphotericin B for injection) is contraindicated in those patients who have demonstrated or have known hypersensitivity to conventional amphotericin B or any other constituents of AmBisome unless, in the opinion of the treating physician, the benefit of therapy outweighs the risk.

WARNINGS

Anaphylaxis has been reported with conventional amphotericin B and other amphotericin B-containing drugs. Anaphylactoid-type reactions have been reported with AmBisome (liposomal amphotericin B for injection). If a severe reaction occurs, the infusion should be immediately discontinued. The patient should not receive further infusions of AmBisome.

AmBisome should be administered primarily to patients with progressive, potentially fatal infections. This drug should not be used to treat the common apparent forms of fungal diseases, which show only positive skin or serologic tests.

PRECAUTIONS

General

As with any amphotericin B-containing product, the drug should be administered by medically trained personnel. During the initial dosing period, patients should be under close clinical observation. AmBisome (liposomal amphotericin B for injection) has been shown to be significantly less toxic than traditional amphotericin B; however, adverse events may still occur. In general, patients should be monitored for any of the adverse events associated with the use of amphotericin B. In particular, caution should be exercised when prolonged therapy is required.

Use in the Elderly

Experience with AmBisome in the elderly (≥ 65 years) is comprised of 71 patients. It has not been necessary to alter the dose of AmBisome for this population. As with most other drugs, elderly patients receiving AmBisome should be carefully monitored. The pharmacokinetics of amphotericin B after administration of AmBisome in elderly patients has not been studied.

Use in Children

Pediatric patients age 1 month to 16 years with presumed fungal infections (empirical therapy), confirmed systemic fungal infections or with visceral leishmaniasis have been treated with AmBisome. In studies

which included 302 pediatric patients administered AmBisome, there was no evidence of any differences in efficacy or safety of AmBisome compared to adults. Since pediatric patients have received AmBisome at doses comparable to those used in adults on a per kilogram body weight basis, no dosage adjustment is required in this population. Safety and effectiveness in pediatric patients below the age of one month has not been established. The pharmacokinetics of amphotericin B after administration of AmBisome in pediatric patients has not been studied.

Use in Pregnancy
Reproduction studies in animals have revealed no evidence of teratogenicity at human therapeutic doses. There have been no adequate and well-controlled studies of AmBisome in pregnant women. Systemic fungal infections have been successfully treated in pregnant women with conventional amphotericin B without obvious effects to the fetus, but the number of case reports has been small. Because animal reproduction studies are not always predictive of human response, and adequate and well-controlled studies have not been conducted in pregnant women, this drug should be administered during pregnancy with caution and only if the potential benefit to the mother outweighs the potential risk to the fetus.

Nursing Mothers
Many drugs are excreted in human milk; however, it is not known whether AmBisome is excreted in human milk. Due to the potential for serious adverse reactions in breastfed infants, a decision should be made whether to discontinue nursing or whether to discontinue the drug, taking into account the importance of the drug to the mother.

Carcinogenicity/Mutagenicity
AmBisome has not undergone testing for mutagenic or carcinogenic potential.

Patients with Special Diseases or Conditions
Hepatic Impairment:
The effect of hepatic impairment on the disposition of AmBisome is not known.

Renal Impairment:
The effect of renal impairment on the disposition of AmBisome has not been studied. However, AmBisome has been successfully administered to patients with preexisting renal impairment (see Clinical Studies section).

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

Renal Dialysis Patients:
The administration of AmBisome should be initiated after dialysis is completed.

Monitoring and Laboratory Tests:
Patient management should include laboratory evaluation of renal, hepatic and hematopoietic function, complete blood counts and serum electrolytes (particularly magnesium and potassium).

Drug-Drug Interactions
No formal clinical studies of drug interactions have been conducted with AmBisome; however, the following drugs are known to interact with amphotericin B and may interact with AmBisome:

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.

Corticosteroids, corticotropin (ACTH) and diuretics:
Concurrent use of corticosteroids, corticotropin (ACTH) or diuretics (loop and thiazide) with amphotericin B may potentiate hypokalemia, which could predispose the patient to cardiac dysfunction. If used concomitantly, serum electrolytes and cardiac function should be closely monitored.

Digitalis glycosides:
Concurrent use may induce hypokalemia and may potentiate digitalis toxicity. When administered concomitantly, serum potassium levels should be closely monitored.

Flucytosine:
Concurrent use of flucytosine with amphotericin-B-containing preparations may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion. Flucytosine should be given concomitantly with AmBisome with caution.

Azoles (e.g., ketoconazole, miconazole, clotrimazole, fluconazole, etc.):
In vitro and *in vivo* animal studies of the combination of amphotericin B and imidazoles suggest that imidazoles may induce fungal resistance to amphotericin B. Combination therapy should be administered with caution, especially in immunocompromised patients.

Leukocyte transfusions:
Acute pulmonary toxicity has been reported in patients simultaneously receiving intravenous amphotericin B and leukocyte transfusions. Leukocyte transfusions should not be given concurrently.

Other nephrotoxic agents:
Concurrent use of amphotericin B and agents such as aminoglycosides, cyclosporine and pentamidine may enhance the potential for drug-induced renal toxicity and should be used only with caution. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications.

Skeletal muscle relaxants:
Amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g., tubocurarine) due to hypokalemia. When administered concomitantly, serum potassium levels should be closely monitored.

Drug-Laboratory Interactions
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.

ADVERSE REACTIONS

The following adverse events are based on the experience of 592 adult patients (295 treated with AmBisome (liposomal amphotericin B for injection) and 297 treated with amphotericin B desoxycholate) and 95 pediatric patients (48 treated with AmBisome and 47 treated with amphotericin B desoxycholate) in Study 94-0-002, a randomized double-blind, multicenter study for the empiric treatment of febrile, neutropenic patients. AmBisome and amphotericin B were infused over two to four hours.

The incidence of common adverse events occurring with either AmBisome or amphotericin B desoxycholate, regardless of relationship to study drug, is shown in Table 2.

Table 2: Empirical Therapy Study 94-0-002 Common (≥ 10% incidence) Adverse Events		
Adverse Event by Body System	**AmBisome n=343 %**	**Amphotericin B n=344 %**
Body as a Whole		
Abdominal pain	19.8	21.8
Asthenia	13.1	10.8
Back pain	12.0	7.3
Blood product transfusion reaction	18.4	18.6
Chills	47.5	75.9
Fever	89.5	91.0
Infection	11.1	9.3
Pain	14.0	12.8
Procedural Complication	19.8	19.8
Sepsis	14.0	11.3
Cardiovascular System		
Chest pain	12.0	11.6
Hypertension	7.9	16.3
Hypotension	14.3	21.5
Tachycardia	13.4	20.9
Digestive System		
Diarrhea	30.3	27.3
Gastrointestinal hemorrhage	9.9	11.3
Nausea	39.7	38.7
Vomiting	31.8	43.9
Metabolic and Nutritional Disorders		
Alkaline phosphatase increased	22.2	19.2
ALT (SGPT) increased	14.6	14.0
AST (SGOT) increased	12.8	12.8
Bilirubinemia	18.1	19.2
BUN increased	21.0	31.1
Creatinine increased	22.4	42.2
Edema	14.3	14.8
Hyperglycemia	23.0	27.9
Hypernatremia	4.1	11.0
Hypervolemia	12.2	15.4
Hypocalcemia	18.4	20.9
Hypokalemia	42.9	50.6
Hypomagnesemia	20.4	25.6
Peripheral edema	14.6	17.2
Nervous System		
Anxiety	13.7	11.0
Confusion	11.4	13.4
Headache	19.8	20.9
Insomnia	17.2	14.2

Table 2: Empirical Therapy Study 94-0-002 Common (≥ 10% incidence) Adverse Events		
Adverse Event by Body System	**AmBisome n=343 %**	**Amphotericin B n=344 %**
Respiratory System		
Cough Increased	17.8	21.8
Dyspnea	23.0	29.1
Epistaxis	14.9	20.1
Hypoxia	7.6	14.8
Lung disorder	17.8	17.4
Pleural effusion	12.5	9.6
Rhinitis	11.1	11.0
Skin and Appendages		
Pruritus	10.8	10.2
Rash	24.8	24.4
Sweating	7.0	10.8
Urogenital System		
Hematuria	14	14

AmBisome was well tolerated. AmBisome had a lower incidence of chills, hypotension, hypertension, tachycardia, hypoxia, hypokalemia, and various events related to decreased kidney function as compared to amphotericin B desoxycholate.

In pediatric patients (16 years of age or less) in this double-blind study, AmBisome, compared to amphotericin B desoxycholate had a lower incidence of hypokalemia (37% versus 55%), chills (29% versus 68%), vomiting (27% versus 55%), and hypertension (10% versus 21%). Similar trends, although with a somewhat lower incidence, were observed in open-label, randomized Study 104-14 involving 205 febrile neutropenic pediatric patients (141 treated with AmBisome and 64 treated with amphotericin B desoxycholate). Pediatric patients appear to have more tolerance than older individuals for the nephrotoxic effects of amphotericin B desoxycholate.

The following adverse events are based on the experience of 244 patients (202 adult and 42 pediatric patients) of whom 85 patients were treated with AmBisome 3 mg/kg, 81 patients were treated with AmBisome 5 mg/kg and 78 patients were treated with amphotericin B lipid complex 5 mg/kg in Study 97-0-034, a randomized, double-blind, multicenter study in febrile, neutropenic patients. AmBisome and amphotericin B lipid complex were infused over two hours.

Patients administered AmBisome (3 mg/kg per day and/or 5 mg/kg per day) had a statistically lower incidence of chills, hypertension, hypotension, tachycardia, increased creatinine, hypoxia, hyperventilation and asthma than those administered amphotericin B lipid complex. These adverse events were 2.5 to 13 times more frequent for patients in the amphotericin B lipid complex group compared with those administered AmBisome. However, confusion was more common (nearly 4 times more frequent) with 3 mg/kg per day AmBisome than with amphotericin B lipid complex.

The incidence of adverse events with statistically significant differences between AmBisome (3 mg/kg and/or 5 mg/kg) and amphotericin B lipid complex treatment groups regardless of relationship to study drug are summarized in Table 3.

Table 3: Empirical Therapy Study 97-0-034 Incidence and p-value† (Fisher's Exact Test)			
	AmBisome 3 mg/kg/day	**AmBisome 5 mg/kg/day**	**Amphotericin B lipid complex**
Total number of patients	85	81	78
Chills / Rigors	40.0% p<0.001	48.1% p<0.001	89.7%
Hypertension	10.6% p=0.037	19.8% p=0.700	23.1%
Hypotension	10.6% p=0.129	7.4% p=0.035	19.2%
Tachycardia	9.4% p=0.020	18.5% p=0.559	23.1%
Creatinine Increased	20.0% p<0.001	18.5% p<0.001	48.7%
Confusion	12.9% p=0.050	8.6% p=0.329	3.8%
Hypoxia	7.1% p=0.020	6.2% p=0.009	20.5%
Hyperventilation	3.5% p=0.197	1.2% p=0.032	9.0%
Asthma	0 p=0.050	1.2% p=0.204	5.1%

† p-values vs amphotericin B lipid complex

In a double-blind, placebo-controlled study of patients undergoing bone marrow transplantation or chemotherapy, there were no significant differences between AmBisome and placebo in the incidence of adverse events.

Study 94-0-013, was a randomized, double-blind, multicenter comparative trial of two doses of AmBisome versus amphotericin B, for a target 14-day induction period. Treatment was followed by fluconazole as consolidation therapy to complete a total of 10 weeks of therapy for the treatment of acute cryptococcal meningitis in AIDS patients. The following adverse events are based on the experience of 267 patients (266 adult and 1 pediatric patient) of whom 86 patients were treated with AmBisome 3 mg/kg/day, 94 patients were treated with AmBisome 6 mg/kg/day and 87 patients were treated with amphotericin B desoxycholate 0.7 mg/kg/day. AmBisome and amphotericin B were infused over two to four hours.

The incidence of adverse events occurring in more than 10% of subjects in one or more treatment arms is provided in Table 4.

Table 4: Incidence of Common (≥ 10% incidence) Non-Infusion Related Adverse Events (Weeks 1-4) Study 94-0-013			
Adverse Event by Body System	**AmBisome 3 mg/kg/day n=86 %**	**AmBisome 6 mg/kg/day n=94 %**	**Amphotericin B 0.7 mg/kg/day n=87 %**
Body as a Whole			
Abdominal pain	7.0	7.4	10.3
Infection	12.8	11.7	6.9
Procedural Complication	8.1	9.6	10.3
Cardiovascular System			
Phlebitis	9.3	10.6	25.3
Digestive System			
Anorexia	14.0	9.6	11.5
Constipation	15.1	14.9	20.7
Diarrhea	10.5	16.0	10.3
Nausea	16.3	21.3	25.3
Vomiting	10.5	21.3	20.7
Hemic and Lymphatic System			
Anemia	26.7	47.9	43.7
Leukopenia	15.1	17.0	17.2
Thrombocytopenia	5.8	12.8	6.9
Metabolic and Nutritional Disorders			
Bilirubinemia	0	8.5	12.6
BUN Increased	9.3	7.4	10.3
Creatinine Increased	18.6	39.4	43.7
Hyperglycemia	9.3	12.8	17.2
Hypocalcemia	12.8	17.0	13.8
Hypokalemia	31.4	51.1	48.3
Hypomagnesemia	29.1	48.9	40.2
Hyponatremia	11.6	8.5	9.2
Liver Function Tests Abnormal	12.8	4.3	9.2
Nervous System			
Dizziness	7.0	8.5	10.3
Insomnia	22.1	17.0	20.7
Respiratory System			
Cough Increased	8.1	2.1	10.3
Skin and Appendages			
Rash	4.7	11.7	4.6

Among non-infusion-related adverse events, overall cardiovascular adverse events and phlebitis were lower in both AmBisome groups as shown in Table 5.

Table 5: Cardiovascular Adverse Events Study 94-0-013			
	AmBisome 3 mg/kg/day	**AmBisome 6 mg/kg/day**	**Amphotericin B 0.7 mg/kg/day**
Total number of patients receiving at least one dose of study drug	86	94	87
Cardiovascular system, any adverse event	23 (27%)	27 (29%)	39 (45%)
Phlebitis	8 (9%)	10 (11%)	22 (25%)

The following adverse events occurred at a significantly higher rate with the 6 mg/kg/day AmBisome dose compared to the 3 mg/kg/day AmBisome dose: overall incidence of hemic and lymphatic system adverse events, anemia, hypokalemia, hypomagnesemia, creatinine increased and bilirubinemia.

Infusion-Related Reactions
In Study 94-0-002, the large, double-blind study of pediatric and adult febrile neutropenic patients, no premedication to prevent infusion-related reaction was administered prior to the first dose of study drug (Day 1). AmBisome-treated patients had a lower incidence of infusion-related fever (17% versus 44%), chills/rigors (18% versus 54%) and vomiting (6% versus 8%) on Day 1 as compared to amphotericin B desoxycholate-treated patients.

The incidence of infusion-related reactions on Day 1 in pediatric and adult patients is summarized in Table 6.

Table 6: Incidence of Day 1 Infusion-Related Reactions (IRR) By Patient Age

	Pediatric Patients (≤ 16 years of age)		Adult Patients (> 16 years of age)	
	AmBisome 3 mg/kg/day	Amphotericin B 0.6 mg/kg/day	AmBisome 3 mg/kg/day	Amphotericin B 0.6 mg/kg/day
Total number of patients receiving at least one dose of study drug	48	47	295	297
Patients with fever† increase ≥1.0°C	6 (13%)	22 (47%)	52 (18%)	128 (43%)
Patients with chills/rigors	4 (8%)	22 (47%)	59 (20%)	165 (56%)
Patients with nausea	4 (8%)	4 (9%)	38 (13%)	31 (10%)
Patients with vomiting	2 (4%)	7 (15%)	19 (6%)	21 (7%)
Patients with other reactions	10 (21%)	13 (28%)	47 (16%)	69 (23%)

† Day 1 body temperature increased above the temperature taken within 1 hour prior to infusion (preinfusion temperature) or above the lowest infusion value (no preinfusion temperature recorded).

Cardiorespiratory events, except for vasodilatation (flushing), during all study drug infusions were more frequent in amphotericin B-treated patients as summarized in Table 7.

Table 7: Incidence of Infusion-Related Cardiorespiratory Events

Event	AmBisome 3 mg/kg/day n = 343	Amphotericin B 0.6 mg/kg/day n = 344
Hypotension	12 (3.5%)	28 (8.1%)
Tachycardia	8 (2.3%)	43 (12.5%)
Hypertension	8 (2.3%)	39 (11.3%)
Vasodilatation	18 (5.2%)	2 (0.6%)
Dyspnea	16 (4.7%)	25 (7.3%)
Hyperventilation	4 (1.2%)	17 (4.9%)
Hypoxia	1 (0.3%)	22 (6.4%)

The percentage of patients who received drugs either for the treatment or prevention of infusion-related reactions (e.g., acetaminophen, diphenhydramine, meperidine and hydrocortisone) was lower in AmBisome-treated patients compared with amphotericin B desoxycholate-treated patients.

In the empirical therapy study, 97-0-034, on Day 1, where no premedication was administered, the overall incidence of infusion-related events of chills/rigors was significantly lower for patients administered AmBisome compared with amphotericin B lipid complex. In addition, a lower incidence of chills/rigors on Day 1 was evident regardless of age, sex, receipt of bone marrow transplant or transplant type, or the

use of immunosuppressants. Fever, chills/rigors and hypoxia were significantly lower for each AmBisome group compared with the amphotericin B lipid complex group. The infusion-related event, hypoxia, was reported for 11.5% of amphotericin B lipid complex-treated patients compared with 0% of patients administered 3 mg/kg per day AmBisome and 1.2% of patients treated with 5 mg/kg per day AmBisome (see Table 8).

Table 8: Incidence of Day 1 Infusion-Related Reactions (IRR) Chills/Rigors Empirical Therapy Study 97-0-034

	AmBisome			Amphotericin B lipid complex 5 mg/kg/day
	3 mg/kg/day	5 mg/kg/day	BOTH	
Total number of patients	85	81	166	78
Patients with Chills/Rigors	16 (18.8%)	19 (23.5%)	35 (21.1%)	62 (79.5%)
Total number with IRR	44 (51.8%)	39 (48.1%)	83 (50.0%)	69 (88.5%)
Patients with fever† ≥1.0°C increase in temperature	20 (23.5%)	16 (19.8%)	36 (21.7%)	45 (57.7%)
Patients with nausea	9 (10.6%)	7 (8.6%)	16 (9.6%)	9 (11.5%)
Patients with vomiting	5 (5.9%)	5 (6.2%)	10 (6.0%)	11 (14.1%)
Patients with other significant reactions	16 (18.8%)	21 (25.9%)	37 (22.3%)	32 (41.0%)
Hypertension	4 (4.7%)	7 (8.6%)	11 (6.6%)	12 (15.4%)
Tachycardia	2 (2.4%)	8 (9.9%)	10 (6.0%)	14 (17.9%)
Dyspnea	4 (4.7%)	8 (9.9%)	12 (7.2%)	8 (10.3%)
Hypoxia	0	1 (1.2%)	1 (<1%)	9 (11.5%)

† Day 1 body temperature increased above the temperature taken within 1 hour prior to infusion (preinfusion temperature) or above the lowest infusion value (no preinfusion temperature recorded). Patients were not administered pre-medications to prevent infusion-related reactions prior to the Day 1 study drug infusion.

In Study 94-0-013, a randomized, double-blind, multicenter trial comparing AmBisome and amphotericin B desoxycholate as initial therapy for cryptococcal meningitis, in 266 adult and one pediatric HIV positive patients, premedications to prevent infusion-related reactions were permitted. The proportion of patients in the amphotericin B group who required medication for the treatment of infusion-related reactions was > 2 times that in the AmBisome group. AmBisome-treated patients again had a lower incidence of fever, chills/rigors and respiratory adverse events as summarized in Table 9.

Table 9: Incidence of Infusion-Related Reactions Study 94-0-013

	AmBisome 3 mg/kg/day	AmBisome 6 mg/kg/day	Amphotericin B 0.7 mg/kg/day
Total number of patients receiving at least one dose of study drug	86	94	87
Patients with fever increase of >1°C	6 (7%)	8 (9%)	24 (28%)
Patients with chills/rigors	5 (6%)	8 (9%)	42 (48%)
Patients with nausea	11 (13%)	13 (14%)	18 (20%)
Patients with vomiting	14 (16%)	13 (14%)	16 (18%)
Respiratory adverse events	0	1 (1%)	8 (9%)

There have been a few reports of flushing, back pain with or without chest tightness, and chest pain associated with AmBisome administration; on occasion, this has been severe. Where these symptoms were noted, the reaction developed within a few minutes after the start of infusion and disappeared rapidly when the infusion was stopped. The symptoms do not occur with every dose and usually do not recur on subsequent administrations when the infusion rate is slowed.

Toxicity and Discontinuation of Dosing
In Study 94-0-002, a significantly lower incidence of grade 3 or 4 toxicity was observed in the AmBisome group compared with the amphotericin B group. In addition, nearly three times as many patients administered amphotericin B required a reduction in dose due to toxicity or discontinuation of study drug due to an infusion-related reaction compared with those administered AmBisome.

In empirical therapy study, 97-0-034, a significantly higher percentage of patients in the amphotericin B lipid complex group discontinued the study drug due to an adverse event than in the AmBisome groups (32% vs 13%, respectively). The incidence of discontinuations due to increased creatinine was significantly higher in the amphotericin B lipid complex group than in the AmBisome 5 mg/kg per day group (10% vs 1%, respectively) or the AmBisome 3 mg/kg per day group (10% vs 2%, respectively). In addition, the incidence of discontinuation was significantly higher in the amphotericin B lipid complex group than in the AmBisome 3 mg/kg per day group due to fever (6% vs 0%, respectively) and in the AmBisome 5 mg/kg per day group due to hypoxia (8% vs 0%, respectively).

Less Common Adverse Events
The following adverse events also have been reported in 2% to 10% of AmBisome-treated patients receiving chemotherapy or bone marrow transplantation or who had HIV disease in six comparative, clinical trials:

Body as a Whole:	abdomen enlarged, allergic reaction, cellulitis, cell-mediated immunological reaction, face edema, graft-versus-host disease, malaise, neck pain, and procedural complication.
Cardiovascular System:	arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, cardiomegaly, hemorrhage, postural hypotension, valvular heart disease, vascular disorder, and vasodilatation (flushing).
Digestive System:	anorexia, constipation, dry mouth/nose, dyspepsia, dysphagia, eructation, fecal incontinence, flatulence, hemorrhoids, gum/oral hemorrhage, hematemesis, hepatocellular damage, hepatomegaly, ileus, liver function test abnormal, mucositis, rectal disorder, stomatitis, ulcerative stomatitis, and veno-occlusive liver disease.
Hemic and Lymphatic System:	anemia, coagulation disorder, ecchymosis, fluid overload, petechia, prothrombin decreased, prothrombin increased, and thrombocytopenia.
Metabolic and Nutritional Disorders:	acidosis, amylase increased, hyperchloremia, hyperkalemia, hypermagnesemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactate dehydrogenase increased, nonprotein nitrogen (NPN) increased, and respiratory alkalosis.
Musculoskeletal System:	arthralgia, bone pain, dystonia, myalgia, and rigors.
Nervous System:	agitation, coma, convulsion, depression, dysesthesia, dizziness, hallucinations, nervousness, paresthesia, somnolence, thinking abnormality, and tremor.

Respiratory System:	asthma, atelectasis, hemoptysis, hiccup, hyperventilation, influenza-like symptoms, lung edema, pharyngitis, pneumonia, respiratory insufficiency, respiratory failure, and sinusitis.
Skin and Appendages:	alopecia, dry skin, herpes simplex, injection site reactions involving pain and inflammation, maculopapular rash, purpura, skin discoloration, skin disorder, skin ulcer, urticaria, and vesiculobullous rash.
Special Senses:	conjunctivitis, dry eyes, and eye hemorrhage.
Urogenital System:	abnormal renal function, acute renal failure, dysuria, renal failure, toxic nephropathy, urinary incontinence, and vaginal hemorrhage.

Postmarketing Adverse Events
The following adverse experiences have been reported infrequently in postmarketing surveillance, in addition to those mentioned above: agranulocytosis, anaphylactic reaction, angioedema, bronchospasm/wheezing, cholestasis, cyanosis/hypoventilation, erythema, epilepsy, fever, generalized edema, headache, hemorrhagic cystitis, hyperbilirubinemia, hypocalcemia, jaundice, increased liver enzymes, leukopenia, multi-organ failure, myocardial infarction, pelvic bleeding, pulmonary edema, renal impairment, retrosternal pain, rhabdomyolysis (associated with hypokalemia), stomach pain, sweating, swelling (face, lips, eyes), tachycardia, urea increase, urticaria.

Clinical Laboratory Values
The effect of AmBisome on renal and hepatic function and on serum electrolytes was assessed from laboratory values measured repeatedly in randomized clinical trials. The laboratory data from the controlled clinical trials previously discussed were used in this analysis. Nephrotoxicity was defined as creatinine values increasing 100% or more over pretreatment levels in pediatric patients and creatinine values increasing 100% or more over pretreatment levels in adult patients provided the peak creatinine concentration was > 1.2 mg/dL. Hypokalemia was defined as potassium levels ≤ 2.5 mmol/L any time during treatment.

The incidence of hepatotoxicity appeared similar in the AmBisome and amphotericin B treatment groups. Hepatotoxicity was defined as significant changes from baseline in serum concentrations of AST (SGOT) or ALT (SGPT). Significant changes were an increase to a value > 5 times baseline in cases where baseline is < 2 times the upper limit of normal, an increase to a value > 3 times baseline in cases where baseline is 2-5 times the upper limit of normal, and an increase to a value > 2 times baseline in cases where baseline is > 5 times the upper limit of normal.

In study 94-0-002 for AmBisome, 18.7% of patients had nephrotoxicity compared with 33.7% for patients treated with conventional amphotericin B. For hypokalemia, 6.7% of AmBisome-treated patients had decreased serum potassium levels compared with 11.6% of patients who received the traditional amphotericin B formulation. For the empirical study 97-0-034, the incidence of nephrotoxicity by all measures was significantly lower, at 14.5%, for patients administered AmBisome compared with 42.5% in patients administered amphotericin B lipid complex.

The incidence of nephrotoxicity in the comparative trial for cryptococcal meningitis, Study 94-0-013, was lower in the combined AmBisome group (3 and 6 mg/kg/day), at 17.8%, compared to those treated with amphotericin B (0.7 mg/kg/day), for which 33.3% of the patients experienced nephrotoxicity.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The toxicity of AmBisome due to overdose has not been defined. Repeated daily doses up to 10 mg/kg in pediatric patients and 15 mg/kg in adult patients have been administered in clinical trials with no reported dose-related toxicity. If an overdose is suspected, discontinue therapy, monitor the patient's clinical status and administer supportive therapy as required. Particular attention should be given to monitoring renal function. Hemodialysis or peritoneal dialysis does not appear to significantly affect the elimination of AmBisome.

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

AmBisome is not interchangeable with other amphotericin products. Different amphotericin products (sodium deoxycholate, liposomal, lipid complex) are not equivalent in terms of pharmacodynamics, pharmacokinetics and dosing. Serious, including fatal, medication errors have occurred with the inadvertent substitution of other amphotericin products for AmBisome. Verify the trade name, common name and dose prior to administration.

AmBisome (liposomal amphotericin B for injection) should be administered by intravenous infusion over a period of approximately 120 minutes. Infusion time may be reduced to approximately 60 minutes in patients in whom the treatment is well tolerated. If the patient experiences discomfort during infusion, the duration of infusion may be increased. The recommended concentration for intravenous infusion is 0.5 mg/mL to 2.0 mg/mL of AmBisome.

The daily dose and duration of therapy of AmBisome should be based on the infecting organism, the patient’s condition and the response to therapy. Treatment should be continued until clinical parameters and laboratory tests indicate that an active fungal infection has been cured or subsided. An inadequate period of treatment may lead to recurrence of active infection. Dose, rate of infusion and duration of treatment may have to be individualized for the needs of specific patients. The recommended initial dosage of AmBisome for each indication for adult, pediatric and special population groups is outlined below and reported in the “Pharmacology” section.

Systemic Mycoses
Patients with a proven systemic infection with *Aspergillus, Candida* and/or *Cryptococcus* species who are refractory to or intolerant to conventional amphotericin B therapy or are renally impaired usually have therapy instituted at 3.0 mg/kg/day, which is increased up to 5.0 mg/kg/day, as required.

Cryptococcal Meningitis in HIV-Infected Patients
HIV-infected patients with cryptococcal meningitis were treated with a dose of 3.0 mg/kg/day or 6.0 mg/kg/day for an average of 14 days. Due to an increased incidence of adverse events with the 6.0 mg/kg/day dose, it is recommended patients be started with a dose of 3.0 mg/kg/day and increase to 6.0 mg/kg/day as required. Because of the high frequency of relapses, chronic suppressive therapy with another agent may be necessary after completion of a treatment course with AmBisome.

Empirical Treatment
For empirical therapy, AmBisome was administered at an initial dose of 3.0 mg/kg/day, and increased or decreased as needed (dose range of 1.5-6.0 mg/kg/day) for 1-53 days at a cumulative dose of 33.4 ± 30.8 mg/kg.

Maximum Dose

In maximum tolerated dose studies in patients with empirical or proven fungal infections, treatment has been administered an average of 9-29 days in adults at doses of 7.5-15.0 mg/kg/day and 8-15 days in children at 2.5-10.0 mg/kg/day without any dose-limiting toxicity detected.

Special Patient Groups

Renal Impairment:
The effect of renal impairment on the disposition of AmBisome has not been studied. AmBisome has been successfully administered to patients with preexisting renal impairment. For renal dialysis patients, AmBisome administration should be initiated after dialysis is completed.

Hepatic Impairment:
The effect of hepatic impairment on the disposition of AmBisome is unknown.

PHARMACEUTICAL INFORMATION

Drug Substance

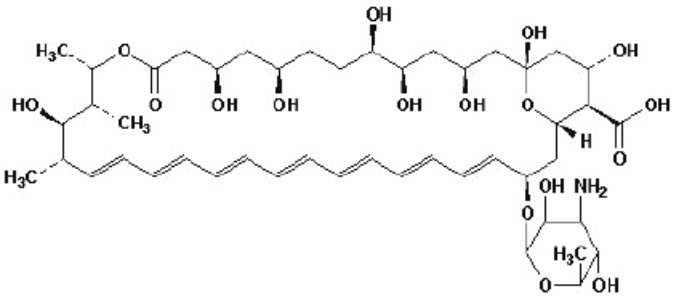
Proper Name: amphotericin B

Chemical Name: [1R-(1R, 3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E, 23E, 25E, 27E, 29E, 31E, 33R*,35S*,36R*,37S*)]-33-[(3-Amino-3,6,dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid (CAS No. 1397-89-3).

Molecular Formula: $C_{47}H_{73}NO_{17}$

Molecular Weight: 924.10

Structural Formula:



Description

Physical Form: Amphotericin B is a yellow to orange powder, commonly described as thin yellow needles.

Solubility: Insoluble in water. Soluble in Dimethy Sulfoxide and Dimethyl formamide.

pKa Values: Approximately 5.7 for the carboxylic acid group. Approximately 10 for the free primary amino group of the mycosamine moiety.

Composition

AmBisome is a sterile, non-pyrogenic lyophilized product for intravenous infusion. Each vial contains 50 mg of amphotericin B, USP, intercalated into a liposomal membrane consisting of approximately 213 mg hydrogenated soy phosphatidylcholine, 52 mg cholesterol, NF, 84 mg distearoyl phosphatidylglycerol, 0.64 mg alpha tocopherol, USP, together with 900 mg sucrose, NF, and 27 mg disodium succinate hexahydrate as buffer. Following reconstitution with Sterile Water for Injection, USP, the resulting pH of the suspension is 5.0-6.0.

Stability and Storage Recommendations

STORAGE OF AMBISOME
Unopened vials of lyophilized material are to be stored between temperatures of 2 to 25°C (36 - 77°F).

STORAGE OF RECONSTITUTED PRODUCT CONCENTRATE
The reconstituted product concentrate may be stored for up to 24 hours at 2-8°C (36-46°F) following reconstitution with Sterile Water for Injection, USP. Do not freeze.

STORAGE OF RECONSTITUTED PRODUCT DILUTED WITH 5% DEXTROSE
Do not freeze. Injection of AmBisome should commence within 6 hours of dilution with 5% Dextrose.

CAUTION: DISCARD partially-used vials.

DIRECTIONS FOR RECONSTITUTION AND DILUTION

READ THIS ENTIRE SECTION CAREFULLY BEFORE BEGINNING RECONSTITUTION

AmBisome must be reconstituted using Sterile Water for Injection, USP (without a bacteriostatic agent). Vials of AmBisome containing 50 mg of amphotericin B are prepared as follows:

Reconstitution:

1. Aseptically add 12 mL of Sterile Water for Injection, USP to each AmBisome vial to yield a preparation containing 4 mg amphotericin B/mL (50 mg/12.9 mL).

   CAUTION: DO NOT RECONSTITUTE WITH SALINE OR ADD SALINE TO THE RECONSTITUTED CONCENTRATION, OR MIX WITH OTHER DRUGS.

   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.

2. **SHAKE THE VIALS VIGOROUSLY** for 30 seconds to completely disperse the AmBisome. AmBisome forms a yellow, translucent suspension.

Dilution:

3. Calculate the amount of reconstituted (4 mg/mL) AmBisome to be further diluted. AmBisome must be diluted with 5% dextrose injection to a final concentration between 0.5 mg/mL and 2.0 mg/mL prior to administration.

Filtration:

4. Withdraw this amount of reconstituted AmBisome into a sterile syringe.

5. Attach the 5-micron filter, provided, to the syringe. Inject the syringe contents through the filter, into the appropriate amount of 5% dextrose injection (use only one filter per vial of AmBisome).

   As with all parenteral drug products, the reconstituted AmBisome should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use material if there is any evidence of precipitation or foreign matter. Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in AmBisome or in the materials specified for reconstitution and dilution.

   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**.

   NOTE: An existing intravenous line must be flushed with 5% Dextrose Injection prior to infusion of AmBisome. If this is not feasible, AmBisome should be administered through a separate line.

Availability of Dosage Forms

AmBisome is supplied as a lyophilized powder in either 20 mL or 30 mL vials. Each vial of AmBisome contains 50 mg of amphotericin B. AmBisome is available as single unit vials in a pack of ten vials in individual cartons. Each carton contains one pre-packaged, disposable sterile 5 micron filter.

MICROBIOLOGY

AmBisome (liposomal amphotericin B for injection) has shown *in vitro* activity equal to amphotericin B (within one dilution) against the following organisms:

- *Aspergillus* species: *fumigatus, flavus*
- *Candida* species: *albicans, glabrata, guillermondi, krusei, lusitaniae, parapsilosis, tropicalis*
- *Cryptococcus neoformans*
- *Fusarium* species
- *Blastomyces dermatitidis*

However, standardized techniques for susceptibility testing of antifungal agents have not been established and results of such studies do not necessarily correlate with clinical outcome.

AmBisome is active in animal models against *Aspergillus fumigatus, Candida albicans, Candida krusei, Candida lusitaniae, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis, Leishmania donvani* and *Leishmania infantum*. The administration of AmBisome in these animal models demonstrated prolonged survival of infected animals and clearance of microorganisms from target organs.

PHARMACOLOGY

Human Pharmacokinetics

The dose of AmBisome (liposomal amphotericin B for injection) is expressed as mg of amphotericin B. The pharmacokinetic profile of AmBisome is based on serum concentrations of amphotericin B.

AmBisome has a pharmacokinetic profile significantly different from traditional amphotericin B. The pharmacokinetic profile of amphotericin B as AmBisome was determined in febrile neutropenic cancer and bone marrow transplant patients who received 1-2 infusions of 1.0 to 7.5 mg/kg/day AmBisome for 3 to 20 days. Noncompartmental analysis provided the most useful pharmacokinetic parameters. The mean terminal half-life ($t_{1/2}$) was approximately 7 hours, reflecting a plasma disposition that may be substantially explained by reticuloendothelial uptake. The mean AUC_{0-24} at steady state was indicative of a nonlinear dosage relationship. The increase in AUC_{0-24}, which exceeded dose proportionality at the three lower doses, is believed to be due to reticuloendothelial saturation and subsequent re-entry of AmBisome into the plasma compartment. An apparent decrease over time in AUC_{0-24} at the highest dose may be indicative of a change in a disposition process (e.g., metabolism and/or elimination). The mean clearance at steady state was independent of dose. Trough concentrations were relatively constant for a given patient and dose, suggesting negligible plasma accumulation. The pharmacokinetic parameters of AmBisome (mean ± SD) after the first dose and at steady state are shown in Table 10.

Table 10: Clinical Pharmacokinetic Parameters of AmBisome

Dose	1 mg/kg/day		2.5 mg/kg/day		5 mg/kg/day		7.5 mg/kg/day	
Day	**1 n=8**	**Last n=7**	**1 n=7**	**Last n=7**	**1 n=12**	**Last n=9**	**1 n=6**	**Last n=4**
PARAMETERS								
C_{max} (μg/mL)	7.3 ± 3.8	12.2 ± 4.9	17.2 ± 7.1	31.4 ± 17.8	57.6 ± 21.0	83.0 ± 35.2	83.7 ± 43.0	62.4 ± 17.7
AUC_{0-24} (μg·hr/mL)	27 ± 14	60 ± 20	65 ± 33	197 ± 183	269 ± 96	555 ± 311	476 ± 371	382 ± 148
$t_{1/2}$ (hr)	10.7 ± 6.4	7.0 ± 2.1	8.1 ± 2.3	6.3 ± 2.0	6.4 ± 2.1	6.8 ± 2.1	8.5 ± 3.9	6.9 ± 0.9
V_d (L/kg)	0.58 ± 0.40	0.16 ± 0.04	0.69 ± 0.85	0.18 ± 0.13	0.22 ± 0.17	0.11 ± 0.08	0.26 ± 0.15	0.20 ± 0.07
Vss (L/kg)	0.44 ± 0.27	0.14 ± 0.05	0.40 ± 0.37	0.16 ± 0.09	0.16 ± 0.10	0.10 ± 0.07	0.18 ± 0.10	0.17 ± 0.05
Cl (mL/hr/kg)	39 ± 22	17 ± 6	51 ± 44	22 ± 15	21 ± 14	11 ± 6	25 ± 22	20 ± 7

Distribution

The mean volume of distribution (Vd) following the initial doses of 1.0, 2.5, 5.0 and 7.5 mg/kg/day was similar to the mean volume of distribution at steady state (Vss) calculated from single dose data. Thus, steady state is attained quickly. Following repeated administration of AmBisome at all four dose levels, the values of V were similar to the corresponding calculated values for Vss on the last day of dosing, indicating an extensive distribution outside of the plasma compartment. Based on total amphotericin B concentrations within a dosing interval (24 hours) after administration of AmBisome, the mean half-life was 7-10 hours. However, based on total amphotericin B concentration measured up to 49 days after dosing of AmBisome, the mean half-life was 100-153 hours. The long terminal elimination half-life is probably due to a slow redistribution from tissues. Although variable, mean trough concentrations of amphotericin B remained relatively constant with repeated dosing administration of the same dose over the range of 1.0-7.5 mg/kg/day, indicating no drug accumulation in the plasma.

Tissue Distribution
Amphotericin B concentrations were determined in selected tissues obtained at autopsy from three patients who were enrolled in an AmBisome compassionate use trial. The patients died within 24 hours of receiving their dose of AmBisome. The liver and spleen contained the highest concentrations of amphotericin B, followed by lung and kidney. Concentrations and percent of total dose of amphotericin B in these tissues are shown for each patient in Table 11. Concentrations in other tissues were very low and represented ≤ 0.1% of the total dose.

Table 11: Distribution of Amphotericin B Following AmBisome Dosing

Patient	AmBisome Dose		Concentration µg/g (% of dose)			
	Daily mg/kg	Cumulative mg	Liver	Spleen	Lung	Kidney
1	3	3428	291 (13.8%)	163 (0.8%)	45.4 (1.3%)	50.0 (0.4%)
2	2.3	900	143 (22.5%)	150 (2.6%)	4.5 (0.4%)	10.6 (0.3%)
3	2.25	906	92.8 (18.4%)	291 (5.5%)	0.5 (0.1%)	7.9 (0.3%)

The tissue concentration data from these patients corroborate nonclinical findings that amphotericin B is selectively concentrated in the reticuloendothelial system (i.e., liver and spleen) following administration as AmBisome.

Metabolism
The metabolic pathways of conventional amphotericin B and AmBisome are unknown.

Excretion
The excretion of AmBisome and conventional amphotericin B have not been studied.

CLINICAL STUDIES

Protocol 104-00 Compassionate Use for Patients with Systemic Fungal Infections and No Alternative Treatment due to Nephrotoxicity, Renal Impairment or Failure of Previous Therapy

AmBisome was evaluated in an open, uncontrolled, multicenter, compassionate use study (Protocol 104-00) in hospitalized patients with systemic fungal infections and no alternative treatment due to nephrotoxicity, renal impairment or failure of previous therapy.

A total of 133 patients, 83 males and 50 females, with a mean age of 38.2 years were enrolled in the study. Reasons for inclusion in this study were: nephrotoxicity from conventional amphotericin B: 49 patients (35%); renal insufficiency: 35 patients (25%); failure of previous therapy: 42 patients (30%) and others/no reason stated: 14 patients (10%). Analysis of data was conducted on three categories of patients, those with definitive, presumptive and undefined fungal infections. Mycological responses for the definitive category (53 evaluable episodes) and clinical success rates (91 episodes) by fungal isolate are presented in Table 12. Duration of treatment and cumulative dose varied considerably with a mean duration of treatment of 24.5 ± 16.0 (SD) days and a mean cumulative dose of 42.2 ± 26.6 mg/kg (SD).

The majority of mycoses treated were due to candida. Analysis of data by enrolling category indicated that eradication rates were not dependent by enrollment reason but neutropenic episodes were eradicated at a lower rate than non-neutropenic episodes.

Table 12: Mycological Eradication and Clinical Success Rates for Infectious Episodes Treated with AmBisome in Compassionate Use Study				
	Aspergillus species	***Candida species***	***Cryptococcus***	**Others**
Mycological Eradication	10/23 (43%)	17/21 (81%)	5/6 (83%)	2/3 (66%)
Clinical Success	21/33 (64%)	38/42 (90%)	8/8 (100%)	8/8 (100%)

Treatment of Cryptococcal Infections in HIV-Infected Patients

HIV-infected patients with disseminated cryptococcosis (including cryptococcal meningitis) have been treated with AmBisome in three studies (Protocols Nos. 94-0-013, 104-09 and 104-03).

A) Study 94-0-013, a randomized, double-blind, comparative multicenter trial, evaluated the efficacy of AmBisome at doses (3.0 and 6.0 mg/kg/day) compared with amphotericin B desoxycholate (0.7 mg/kg/day) for the treatment of cryptococcal meningitis in 266 adult and one pediatric HIV positive patients (the pediatric patient received amphotericin B desoxycholate). Patients received study drug once daily for an induction period of 11 to 21 days. Following induction, all patients were switched to oral fluconazole at 400 mg/day for adults and 200 mg/day for patients less than 13 years of age to complete 10 weeks of protocol-directed therapy. Success was defined as CSF culture conversion. For mycological evaluable patients (defined as all randomized patients who received at least one dose of study drug, had a positive baseline CSF culture and had at least one follow-up culture), success was evaluated at week 2 (i.e., 14 ± 4 days) and after the 10-week consolidation period. Success rates at 2 weeks for AmBisome and amphotericin B desoxycholate were equivalent (two-sided 95% CI for the difference in the week 2 mycological success rates [AmBisome combined - amphotericin B desoxycholate] was within ± 20%). Results are summarized in Table 13.

Table 13: Mycological Success Rate (CSF Culture Conversion) Study 94-0-013			
	AmBisome 3 mg/kg/day	**AmBisome 6 mg/kg/day**	**Amphotericin B 0.7 mg/kg/day**
Success at Week 2	35/60 (58.3%) 97.5% CI* = -9.4%, +31.0%	36/75 (48%) 97.5% CI* = -18.8%, +19.8%	29/61 (47.5%)

* 97.5% Confidence Interval for the difference between AmBisome and amphotericin B success rates. A negative value is in favor of amphotericin B. A positive value is in favor of AmBisome.

Success at 10 weeks was defined as clinical success at week 10 plus CSF culture conversion at or prior to week 10. Success rates at 10 weeks in patients with positive baseline culture for cryptococcus species are summarized in Table 14 and show that the efficacy of AmBisome 6 mg/kg/day approximates the efficacy of the amphotericin B desoxycholate regimen. These data do not support the conclusion that AmBisome 3 mg/kg/day is comparable in efficacy to amphotericin B desoxycholate. The table also presents 10-week survival rates for patients treated in this study.

Table 14: Success Rates and Survival Rates at Week 10, Study 94-0-013			
	AmBisome 3 mg/kg/day	**AmBisome 6 mg/kg/day**	**Amphotericin B 0.7 mg/kg/day**
Success in patients with documented cryptococcal meningitis	27/73 (37%) 97.5% CI* = -33.7%, +2.4%	42/85 (49%) 97.5% CI* = -20.9%, +14.5%	40/76 (53%)
Survival Rates	74/86 (86%) 97.5% CI* = -13.8%, +8.9%	85/94 (90%) 97.5% CI* = -8.3%, +12.2%	77/87 (89%)

* 97.5% Confidence Interval for the difference between AmBisome and amphotericin B success rates. A negative value is in favor of amphotericin B. A positive value is in favor of AmBisome.

B) In protocol 104-09, which was an open, comparative study, 30 HIV-infected patients with cryptococcal meningitis were randomized to receive a 3-week treatment with either AmBisome 4 mg/kg/day (15 patients) or amphotericin B 0.7 mg/kg/day (13 patients). All patients completing the initial three weeks of study continued treatment with fluconazole 400 mg/day for an additional seven weeks. The investigators were free to choose maintenance therapy to prevent relapses of cryptococcal infection, but fluconazole 200 mg/day was recommended.

In this small study, significantly more AmBisome than conventional amphotericin B patients had a mycological response within the first 14 days (p=0.01 summarized in Table 15). The median time to mycological response was 7-14 days for AmBisome and >21 days for amphotericin B. One AmBisome patient had a mycological relapse at week 3, but was successfully switched to fluconazole. None of the patients in either group experienced a late mycological relapse (10-week assessment). Clinical response was comparable in both groups (≥ 80%).

Table 15: Clinical & Mycological Response			
Response	**AmBisome 4 mg/kg/day**	**Amphotericin B 0.7 mg/kg/day**	**p-Value**
Clinical			
3 weeks	12/15 (80%)	11/13 (85%)	1.0
10 weeks	13/15 (87%)	10/12 (83%)	ND
Mycological			
1 week	6/15 (40%)	1/12 (8.3%)	0.09
2 weeks	10/15 (67%)	1/9 (11%)*	0.01
3 weeks	11/15 (73%)	3/8 (38%)	0.18
10 weeks	11/11 (100%)	8/8 (100%)	ND

* Some patients in the amphotericin B group refused to undergo lumbar puncture at 14 and 21 days.

C) In Protocol No. 104-03, an open-label, uncontrolled multicenter study, 24 HIV-infected patients (27 infectious episodes) who were hospitalized with a primary episode of cryptococcosis (including cryptococcal meningitis) were treated with AmBisome (4 mg/kg/day) until the infection resolved or the patient was withdrawn from the study. Mycological and clinical responses in 16 evaluable episodes are summarized below:

Efficacy Results for 16 Evaluable Episodes:

Overall Mycological Response	Eradication:	11/16 (69%)
Clinical Response	Cured:	12/16 (75%)
	Improved:	3/16 (19%)

Cryptococcal Meningitis:

Mycological Response	Eradication:	8/13 (62%)
Clinical Response	Cured:	9/13 (69%)
	Improved:	3/13 (23%)

Five (5) of the 16 episodes (31.3%) were eradicated in two weeks and the remaining 6 within 5 weeks. Overall, the median duration (standard deviation) of treatment was 26.6 (±12.6) days and the mean cumulative dose was 72.4 (±41.7) mg/kg. There was no adequate follow-up for relapses; two patients were found to have relapses and were again treated with AmBisome, 1 once and 1 twice.

Empirical Therapy

A) Study 94-0-002, a randomized, double-blind, comparative multicenter trial, evaluated the efficacy of AmBisome initiated at a dose of 3 mg/kg/day and increased or decreased as needed (1.5-6.0 mg/kg/day) compared with amphotericin B desoxycholate initiated at a dose of 0.6 mg/kg/day and increased or decreased as needed (0.3-1.2 mg/kg/day) in the empirical treatment of 687 adult and pediatric neutropenic patients who were febrile despite having received at least 96 hours of broad spectrum antibacterial therapy. Therapeutic success required (a) resolution of fever during the neutropenic period, (b) absence of an emergent fungal infection, (c) patient survival for at least 7 days post therapy, (d) no discontinuation of therapy due to toxicity or lack of efficacy, and (e) resolution of any study-entry fungal infection.

The overall therapeutic success rates for AmBisome and amphotericin B desoxycholate were equivalent (two sided 95% CI for the difference [AmBisome-amphotericin B] was within ±10%). Results are summarized in Table 16.
Note: The categories presented below are not mutually exclusive.

Table 16: Empirical Therapy in Febrile Neutropenic Patients: Randomized, Double-Blind Study in 687 Patients

	AmBisome 3 mg/kg/day	Amphotericin B 0.6 mg/kg/day
Number of patients receiving at least one dose of study drug	343	344
Overall Success†	171 (49.9%)	169 (49.1%)
Fever resolution during neutropenic period	199 (58.0%)	200 (58.1%)
No treatment-emergent fungal infection	300 (87.5%)	301 (87.5%)
Survival through 7 days post study drug	318 (92.7%)	308 (89.5%)
Study drug not prematurely discontinued due to toxicity or lack of efficacy*	294 (85.7%)	280 (81.4%)

† The 95% confidence interval for overall success: -6.8%, +8.2%.
* 8 and 10 patients, respectively, were treated as failures due to premature discontinuation alone.

This therapeutic equivalence had no apparent relationship to the use of prestudy antifungal prophylaxis or concomitant granulocytic colony-stimulating factors, baseline risk factors (high risk defined as (1) had within the previous 3 months, a prior febrile, neutropenic episode treated with systemic amphotericin B therapy, (2) had received an allogeneic bone marrow transplantation or (3) were receiving chemotherapy for a relapse of acute non-lymphocytic leukemia) or age (< 13 years vs ≥ 13 years).

The incidence of mycologically-confirmed and clinically diagnosed, emergent fungal infections are presented in Table 17. The incidence of proven emergent fungal infections was significantly lower in the AmBisome treatment groups.

Table 17: Empirical Therapy in Febrile Neutropenic Patients: Emergent Fungal Infections

	AmBisome 3 mg/kg/day	Amphotericin B 0.6 mg/kg/day
Number of patients receiving at least one dose of study drug	343	344
Mycologically-confirmed fungal infection	11 (3.2%)	27 (7.8%)
Clinically diagnosed fungal infection	32 (9.3%)	16 (4.7%)
Total emergent fungal infections	43 (12.5%)	43 (12.5%)

Mycologically-confirmed fungal infections at study entry were cured in 8 of 11 patients in the AmBisome group and 7 of 10 in the amphotericin B group.

B) Two supportive, prospective, randomized, open label, comparative multicenter studies examined the efficacy of two dosages of AmBisome (1 and 3 mg/kg/day) compared to amphotericin B desoxycholate (1 mg/kg/day) in the treatment of neutropenic patients with presumed fungal infections. These patients were undergoing chemotherapy as part of a bone marrow transplant or had hematological disease. Study 104-10 enrolled adult patients (n=134). Study 104-14 enrolled pediatric patients (n=214). Both studies support the efficacy equivalence of AmBisome and amphotericin B as empirical therapy in febrile neutropenic patients.

Clinical Laboratory Values

The effect of AmBisome on renal and hepatic function and on serum electrolytes was assessed from laboratory values measured repeatedly in Study 94-0-002. Nephrotoxicity was defined as creatinine values increasing 100% or more over pretreatment levels in pediatric patients, and creatinine values increasing 100% or more over pretreatment levels in adult patients, provided the peak creatinine concentration was > 1.2 mg/dL. Hypokalemia was defined as potassium levels ≤ 2.5 mmol/L any time during treatment.

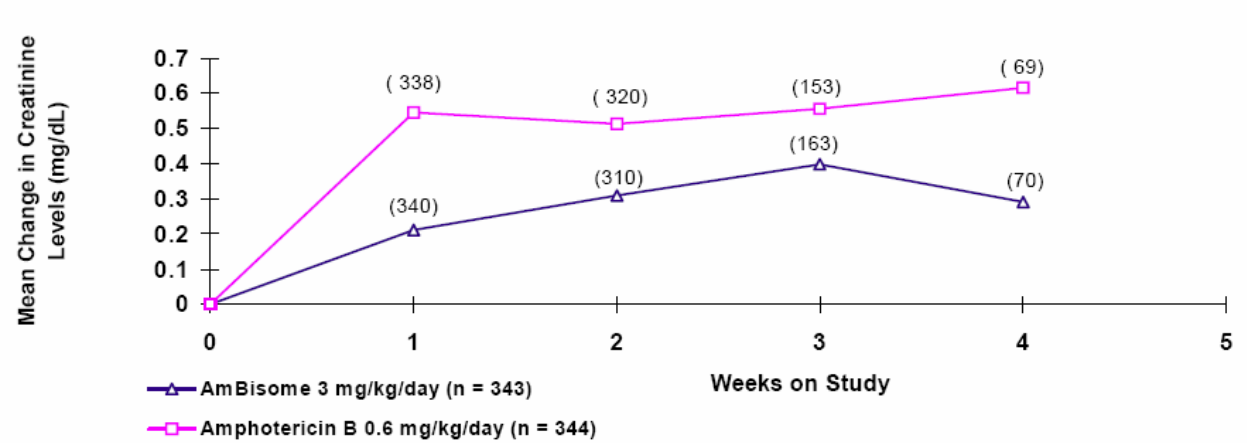
Incidence of nephrotoxicity, mean peak serum creatinine concentration, mean change from baseline in serum creatinine, and incidence of hypokalemia in the double-blind randomized study were significantly lower in the AmBisome group as summarized in Table 18.

Table 18: Study 94-0-002 Laboratory Evidence of Nephrotoxicity

	AmBisome 3 mg/kg/day	Amphotericin B 0.6 mg/kg/day
Total number of patients receiving at least one dose of study drug	343	344
Nephrotoxicity	64 (18.7%)	116 (33.7%)
Mean peak creatinine	1.24 mg/dL	1.52 mg/dL
Mean change from baseline in creatinine	0.48 mg/dL	0.77 mg/dL
Hypokalemia	23 (6.7%)	40 (11.6%)

The effect of AmBisome (3 mg/kg/day) vs. amphotericin B (0.6 mg/kg/day) on renal function in adult patients enrolled in this study is illustrated in Figure 2.

Figure 2: Mean Change in Creatinine Over Time in Study 94-0-002



In empirical therapy study 97-0-034, the incidence of nephrotoxicity by all measures was significantly lower for patients administered AmBisome (individual dose groups and combined) compared with amphotericin B lipid complex. Lower nephrotoxicity was evident regardless of age, sex, receipt of bone marrow transplant, transplant type, or use of immunosuppressants (see Table 19).

Table 19: Incidence of Nephrotoxicity Empirical Therapy Study 97-0-034

	AmBisome			Amphotericin B lipid complex 5 mg/kg/day
	3 mg/kg/day	5 mg/kg/day	BOTH	
Total number of patients	85	81	166	78
Number with nephrotoxicity				
1.5X baseline serum creatinine value	25 (29.4%)	21 (25.9%)	46 (27.7%)	49 (62.8%)
2X baseline serum creatine value	12 (14.1%)	12 (14.8%)	24 (14.5%)	33 (42.3%)
Peak Serum Creatinine (mg/dL)				
Mean ± SD Median (range)	1.3 ± 1.0 1.1 (0.3-6.3)	1.2 ± 0.6 0.9 (0.3-3.3)	1.2 ± 0.8 1.0 (0.3-6.3)	1.8 ± 1.2 1.5 (0.5-6.0)
Change from baseline to peak serum creatinine value (mg/dL)				
Mean ± SD Median (range)	0.5 ± 0.8 0.3 (0-4.7)	0.4 ± 0.4 0.2 (-0.1-2.1)	0.5 ± 0.7 0.3 (-0.1-4.7)	1.0 ± 1.0 0.7 (0-5.3)

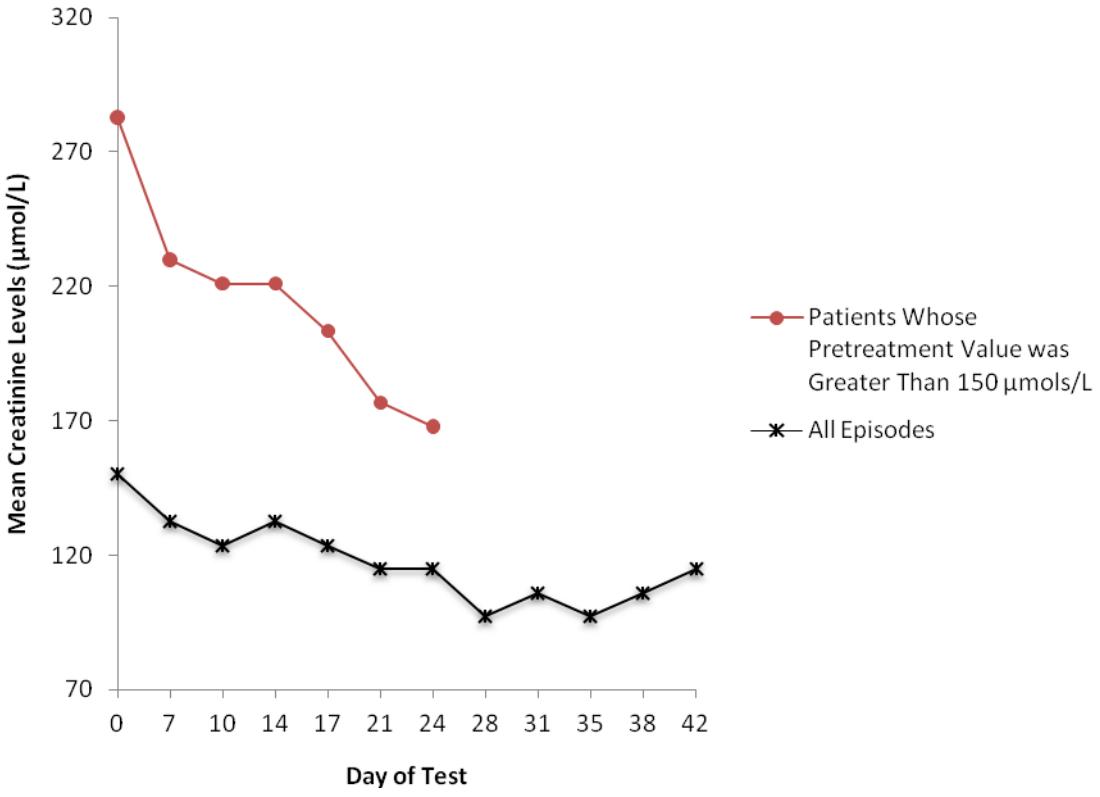
SD: standard deviation

The incidence of nephrotoxicity in Study 94-0-013, comparative trial in cryptococcal meningitis was lower in the AmBisome groups as shown in Table 20.

Table 20: Laboratory Evidence of Nephrotoxicity Study 94-0-013			
	AmBisome 3 mg/kg/day	**AmBisome 6 mg/kg/day**	**Amphotericin B 0.7 mg/kg/day**
Total number of patients receiving at least one dose of study drug	86	94	87
Nephrotoxicity	12 (14%)	20 (21%)	29 (33%)
Mean peak creatinine	1.7 mg/dL	1.7 mg/dL	1.9 mg/dL
Mean change from baseline in creatinine	0.6 mg/dL	0.7 mg/dL	0.9 mg/dL
Hypokalemia	1 (1.2%)	3 (3.2%)	3 (3.4%)

The following graph (Figure 3) shows the average serum creatinine levels in the compassionate use study and shows that there is a drop from pretreatment levels for all patients, especially those with elevated (≥150 µmol/L) pretreatment creatinine levels.

Figure 3: Mean Creatinine Levels Over Time



Animal Pharmacology

Several *in vitro* studies show that amphotericin B in AmBisome is less toxic to mammalian cells than the conventional desoxycholate formulation of amphotericin B. For example, when washed human red cells were incubated with conventional amphotericin B at a concentration of 1 µg/mL, over 90% of the cells were lysed. In contrast, amphotericin B as AmBisome caused a maximum of 6% lysis even at a

concentration of 100 µg/mL. These results show that AmBisome has virtually no interaction with red blood cells.

The cytotoxic effects of AmBisome and amphotericin B in canine kidney cells and murine macrophages were compared using assays to measure DNA synthesis, protein synthesis and mitochondrial activity. AmBisome was approximately eight-fold less toxic than amphotericin B to the kidney cells and approximately two-fold less toxic to macrophages. The increased sensitivity of the latter cells may be due to phagocytic activity of macrophages, which is not a characteristic of kidney cells.

Available experimental evidence suggests that circulating intact AmBisome liposomes can reach sites of fungal infection and accumulate there. Mice infected with *Candida albicans* were injected with either fluorescently labelled AmBisome, fluorescently labelled liposomes without drug or free fluorescent dye. Fluorescence was relatively more intense at the sites of fungal infection in kidneys from mice treated with either of the fluorescently labelled liposome preparations. Kidneys from animals treated with free fluorescent dye showed red fluorescence throughout the entire kidney in extracellular spaces, but not within cells. The observations suggested that liposomes with or without amphotericin B were preferentially localizing at the site of infection in the kidneys of mice infected with *C. albicans*.

In a similar experiment, liposomes with and without amphotericin B were seen to bind to the yeast cell wall, only the liposomes containing amphotericin B were shown to penetrate the cell wall of both extracellular and intracellular forms of susceptible fungi leading to fungal cell death.

In vitro cultures of macrophages infected with *Candida glabrata* were used to demonstrate that AmBisome can be phagocytized by these macrophages and that the liposomal amphotericin B could in turn kill the intracellular yeast. After incubating fluorescently labelled AmBisome or liposomes without drug for five hours with infected macrophages, microscopic examinations revealed that both labelled preparations had been taken up by the macrophages, and the liposomes had been disrupted. Yeast cell viability in the fluorescent AmBisome macrophage culture was reported to be 29% whereas 91% of the intracellular yeasts were viable in fluorescent liposome-without-drug-treated macrophages.

Studies to evaluate the potential for enzyme induction by AmBisome have not been carried out. Similarly, secondary pharmacology studies have not been carried out.

Pharmacokinetics

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 compared with conventional amphotericin B. Higher levels of amphotericin B were achieved in hepatic and splenic tissues with AmBisome in both mice and rats. In rats, amphotericin B levels in renal tissues were 5 to 10-fold lower for AmBisome, compared to conventional amphotericin B after repeated administration for 28 days. For other organs, tissue levels of amphotericin B were similar for both formulations (see Table 21).

Table 21: Rat tissue accumulation of amphotericin B after 28 treatments with conventional amphotericin B or AmBisome				
Daily Treatment	**Kidney (µg/g)**	**Liver (µg/g)**	**Spleen (µg/g)**	**Lung (µg/g)**
Conventional Amphotericin B				
0.5 mg/kg	3.50 ± 0.58	18.0 ± 3.5	3.78 ± 0.29	1.41 ± 0.26
1.0 mg/kg	6.41 ± 0.31	31.8 ± 8.3	37.1 ± 8.2	4.56 ± 0.95
AmBisome				
0.5 mg/kg	0.36 ± 0.10	62.5 ± 6.1	20.2 ± 4.4	0.61 ± 0.13
1.0 mg/kg	1.01 ± 0.16	83.9 ± 17.9	54.3 ± 8.0	1.84 ± 0.26
3.0 mg/kg	3.21 ± 0.44	97.4 ± 16.7	127.2 ± 30.8	4.94 ± 1.10
5.0 mg/kg	7.10 ± 0.89	346.9 ± 46.5	396.1 ± 49.4	10.35 ± 1.02

TOXICOLOGY

Acute Toxicology

Female C57BL/6 mice were used to evaluate the acute toxicity of AmBisome (liposomal amphotericin B for injection) in safety tests of production batches because of this murine strain's high sensitivity to amphotericin B (LD_{50}: 2.3 mg/kg). Using the Safety Test for AmBisome (based on USP XXII, <88> Safety Tests-General), the LD_{10} of AmBisome was >100 mg/kg. Acute IV safety testing of 30 AmBisome batches indicated a median LD_{50} of 150 mg/kg for AmBisome (range: 133 to >160 mg/kg). In contrast, conventional amphotericin B doses of 2.2 to 2.6 mg/kg caused immediate death.

In female Harlan Sprague-Dawley rats, the LD_{50} of AmBisome was calculated as 58.2 mg/kg, whereas it was 1.51 mg/kg for conventional amphotericin B. When AmBisome was tested for toxicity in female Charles River CD rats, lethalities occurred after single intravenous doses as low as 14 mg/kg. Collective results from several exploratory experiments showed that these lethalities were due to severe hepatocellular necrosis, which appeared to be both gender and substrain specific. Study results are summarized in Table 22.

Table 22: Acute Toxicology						
Species	**No./ Group**	**Sex**	**Route**	**Dose Range (mg/kg/day)**	**Overt Signs of Toxicity**	**LD_{50} (mg/kg/day)**
Mouse C57BL/6	10	F	IV	100-160	Lethargy; weight loss; death	150
Rat Sprague-Dawley	5	F	IV	45-80	Lethargy; weight loss; death	58
Rat Charles River CD	2-5	F	IV	14-36	50-100% deaths, (females)	ND
	2-5	M	IV	70-101	< 20% weight loss; no deaths (males)	

Subchronic Toxicity

The nonclinical subchronic toxicity of AmBisome was determined in mice, rats, rabbits and dogs. In all cases, AmBisome was administered as a single daily intravenous injection.

Since CD rats were found to be very sensitive to the toxic effects of AmBisome, this strain was used in a 30-day study in rats. AmBisome was administered over a dose range of 1-20 mg/kg. Deaths occurred in 12 of 25 females at the high dose of 20 mg/kg, and these all occurred before the third dose was administered. Severe hepatocellular necrosis was implicated as the cause of death. Surviving animals showed minimal overt signs of toxicity.

Pilot studies in rats used doses up to 75 mg/kg/day. In one 30-day pilot study in female Sprague-Dawley rats, AmBisome at 25, 50 and 75 mg/kg/day caused 10, 50 and 90% lethality, respectively. Plasma

creatinine levels were normal or only slightly elevated, suggesting that the lethalities were not due to cumulative nephrotoxicity, which is the benchmark subchronic toxicity of conventional amphotericin B. In a second pilot study in CD rats, AmBisome was administered at doses of 15 to 75 mg/kg/day. Histologic examination of tissues revealed that female rats dying after a single treatment had marked hepatic necrosis.

AmBisome toxicity was evaluated in female rabbits receiving a dose of 5 mg/kg/day for 28 days. This study compared the effects of AmBisome to conventional amphotericin B at 1 mg/kg/day for 28 days. The results showed that AmBisome was less nephrotoxic but somewhat more hepatotoxic than conventional drug given at one-fifth the dose.

A 30-day subchronic toxicity study of AmBisome was conducted in dogs treated for 30 days over a dose range of 0.25 to 16 mg/kg/day. Overt toxicities, including > 25% weight loss, were noted for all animals in the 16 mg/kg treatment group and in three of five males and four of five females in the 8 mg/kg group. Both males and females receiving amphotericin B as AmBisome at ≥ 4 mg/kg/day had dose-dependent elevations in plasma urea and creatinine levels. These observations are consistent with cumulative nephrotoxicity.

A 91-day toxicity study was conducted in rats at doses of 1 mg/kg/day, 4 mg/kg/day and 12 mg/kg/day amphotericin B as AmBisome. The results of this study indicate that the target organs for toxicity were defined as the liver (necrosis) and the kidney (transitional cell hyperplasia). The no-observable effect level (NOEL) for the intravenous administration of AmBisome for 91 days was below 1 mg/kg/day.

Reproductive and Developmental Toxicity
AmBisome (liposomal amphotericin B for injection) was determined to be non-teratogenic based on studies in rats and rabbits outlined in Table 23. (NOTE: In the Table, NOEL refers to No-Observable Effects Level).

Table 23: Reproduction and Developmental Toxicity			
Reproductive Study	**Daily Dose (mg/kg)**	**Findings**	
		Maternal	**Developmental**
Segment I Rat (Study No.: TX954006) (20/sex/group)	Placebo	None	None
	5, 10	Prolonged diestrus; decreased food consumption and weight. General toxicity NOEL < 5 mg/kg; reproductive toxicity NOEL = 5 mg/kg	None
	15	Prolonged diestrus; decreased number of corpora lutea; 7 deaths within 4 days with marked necrosis of hepatic cells; decreased food consumption and weight. Paternal: decreased food consumption and weight in 5, 10 and 15 mg/kg groups.	Decreased number of live embryos.
Segment II Rat (Study No.: TX944008) (23-25/group)	Placebo	None	None
	5	One death from hemorrhage from uterus. In surviving dams; slight hemorrhage from vagina in one dam. Maternal toxicity NOEL = 5 mg/kg; fetal toxicity NOEL = 5 mg/kg.	None
	10, 15	One death at 15 mg/kg/day; no findings indicative of cause of death. In surviving dams: decrease in mean body weight, body weight gain, food consumption; slight hemorrhage from vagina of one dam at 15 mg/kg/day; white foci in liver and or kidney of several dams.	None
Segment II Rabbit (Study No.: TX944009) (17-18/group)	Placebo	One death. Dark red foci in lung and retention of pleural fluid observed upon necropsy.	None
	3	None. Considered maternal non-toxic dose.	None
	7, 16	Decrease in mean body weight, body weight gain. One death at 7 mg/kg/day; dark red foci observed in lung. Two dams at 7 mg/kg/day and 11 dams at 16 mg/kg/day aborted; food consumption and body weight decreased markedly in these animals. Fetal toxicity NOEL = 16 mg/kg/day.	None

Mutagenicity/Carcinogenicity
AmBisome has not undergone testing for mutagenic or carcinogenic potential.

Special Studies
Intravenous administration of conventional amphotericin B can be accompanied by local adverse reactions including phlebitis and thrombophlebitis. AmBisome has been tested specifically for local tolerance in three studies. AmBisome was tested in rabbits for local irritation or inflammation after intradermal injection. AmBisome and liposomes without drug did not cause local irritation or inflammation under the conditions of the test. In a rat study, AmBisome was compared to conventional amphotericin B for local tolerance after being injected paravenously and subcutaneously. AmBisome was less irritating than conventional amphotericin B and did not cause serious inflammation when injected outside a vein. In a second rat study, the observation period was extended to seven days post-injection. After observation, pathological evaluation showed that all articles caused some degree of local inflammation, but by day 7, effects were resolved. A liposome formulation similar to that of AmBisome was evaluated in guinea pigs for its potential to cause active systemic anaphylaxis. No animals became

sensitized or displayed signs of active systemic anaphylaxis. These results suggest that the AmBisome lipids are unlikely to elicit a hypersensitivity reaction.

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