

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-740/SE1-002

APPROVAL LETTER

NDA 50-740/S-002

JUN 16 2000

Fujisawa Healthcare, Inc.
Attention: Mr. Robert M. Reed
Assistant Director, Regulatory Affairs
3 Parkway North Center
Deerfield, IL 60014

Dear Mr. Reed:

Please refer to your supplemental new drug application dated July 6, 1999, received July 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AmBisome[®] (amphotericin B) liposome for injection, 50 mg/vial.

We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated as follows.

September 1, 1999	October 19, 1999	June 6, 2000
October 1, 1999	April 28, 2000	June 15, 2000
October 15, 1999	May 26, 2000	

This supplemental new drug application provides for the use of AmBisome[®] (amphotericin B) liposome for injection, for treatment of cryptococcal meningitis in HIV infected patients.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text submitted June 15, 2000. Accordingly, the application is approved effective on the date of this letter. The final printed labeling (FPL) must be identical to the draft package insert submitted June 15, 2000.

Please submit 20 copies of the FPL as soon as they are available, in no case more than 30 days after they are printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA 50-740/S-002." Approval of this submission by FDA is not required before the labeling is used.

We acknowledge receipt of your submissions dated June 21, 1999 (submitted to [redacted] for Phase 4 Commitments 1 and 2) and July 6, 1999 (submitted to NDA 50-740 for Phase 4 Commitment 3), regarding the following Phase 4 Commitments listed in the August 11, 1997 AmBisome[®] approval letter:

1. Completion of study 96-0-021 in pediatric patients evaluating the maximum tolerated dose of AmBisome[®]. Projected completion: 2nd qtr '98.
2. Completion of study 96-0-017 in adult patients evaluating the maximum tolerated dose of AmBisome[®]. Projected completion: 1st qtr '98.
3. Completion of study 94-0-013 evaluating AmBisome[®] in the treatment of cryptococcal meningitis. Projected completion: 2nd qtr '99.

We have completed review of your Phase 4 data and conclude that the above commitments have been fulfilled.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Leo Chan, Regulatory Project Manager, at
(301) 827-2127.

Sincerely,

RS/ 6/16/00

Renata Albrecht, M.D.

Acting Director

Division of Special Pathogen and
Immunologic Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-740/SE1-002

APPROVED DRAFT LABELING



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4 Revised: June 2000 83040119903

5 **AmBisome®**

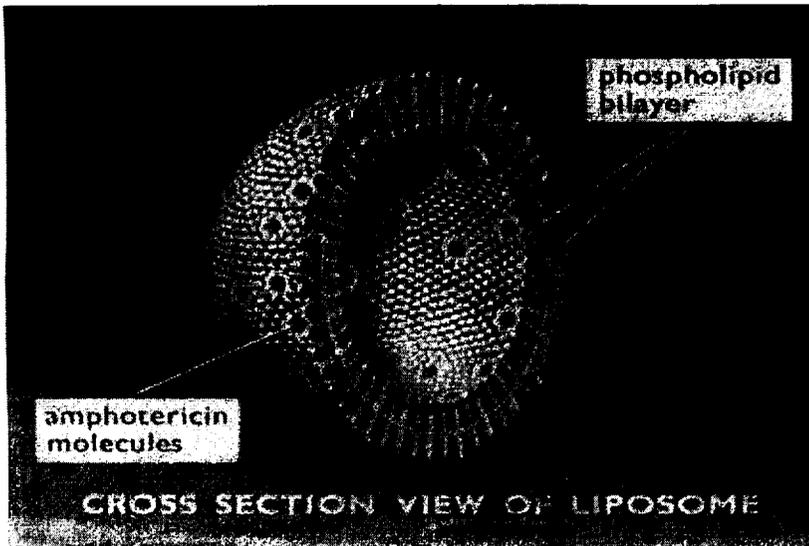
6 (amphotericin B) liposome for injection

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8 **DESCRIPTION:**

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

15 AmBisome is a true single bilayer liposomal drug delivery system. Liposomes are closed,
16 spherical vesicles created by mixing specific proportions of amphophilic substances such as
17 phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer
18 membranes when hydrated in aqueous solutions. Single bilayer liposomes are then formed by
19 microemulsification of multilamellar vesicles using a homogenizer. AmBisome consists of these
20 unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. Due to the nature
21 and quantity of amphophilic substances used, and the lipophilic moiety in the amphotericin B molecule,
22 the drug is an integral part of the overall structure of the AmBisome liposomes. AmBisome contains
23 true liposomes that are less than 100 nm in diameter. A schematic depiction of the liposome is presented
24 below.



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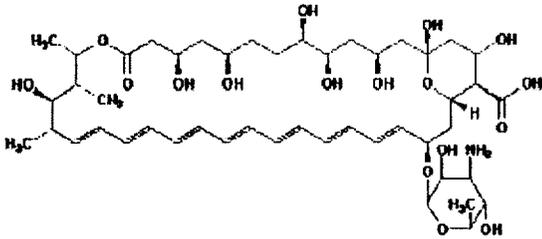
Note: Liposomal encapsulation or incorporation into a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated drug or non-lipid associated drug. In addition, different liposomal or lipid-complex products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect the functional properties of these drug products.

Amphotericin B is a macrocyclic, polyene, antifungal antibiotic produced from a strain of *Streptomyces nodosus*. Amphotericin B is designated chemically as:

[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).

Amphotericin B has a molecular formula of $C_{47}H_{73}NO_{17}$ and a molecular weight of 924.09.

1 The structure of amphotericin B is shown below:



2

3 **MICROBIOLOGY:**

4 **Mechanism of Action**

5 Amphotericin B, the active ingredient of AmBisome, acts by binding to the sterol component of a cell
6 membrane leading to alterations in cell permeability and cell death. While amphotericin B has a higher
7 affinity for the ergosterol component of the fungal cell membrane, it can also bind to the cholesterol
8 component of the mammalian cell leading to cytotoxicity. AmBisome, the liposomal preparation of
9 amphotericin B, has been shown to penetrate the cell wall of both extracellular and intracellular forms of
10 susceptible fungi.

11

12 **Activity *In Vitro* and *In Vivo***

13 AmBisome has shown *in vitro* activity comparable to amphotericin B against the following organisms:
14 *Aspergillus* species (*A. fumigatus*, *A. flavus*), *Candida* species (*C. albicans*, *C. krusei*, *C.*
15 *lusitaniae*, *C. parapsilosis*, *C. tropicalis*), *Cryptococcus neoformans*, and *Blastomyces*
16 *dermatitidis*. However, standardized techniques for susceptibility testing of antifungal agents have not
17 been established and results of such studies do not necessarily correlate with clinical outcome.

18 AmBisome is active in animal models against *Aspergillus fumigatus*, *Candida albicans*,
19 *Candida krusei*, *Candida lusitaniae*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*,
20 *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Leishmania*
21 *donovani*, and *Leishmania infantum*. The administration of AmBisome in these animal models
22 demonstrated prolonged survival of infected animals, reduction of microorganisms from target organs, or
23 a decrease in lung weight.

24

1 **Drug Resistance**

2 Mutants with decreased susceptibility to amphotericin B have been isolated from several fungal species
3 after serial passage in culture media containing the drug, and from some patients receiving prolonged
4 therapy. Drug combination studies *in vitro* and *in vivo* suggest that imidazoles may induce resistance
5 to amphotericin B. However, the clinical relevance of drug resistance has not been established.

6

7 **CLINICAL PHARMACOLOGY:**

8 **Pharmacokinetics**

9 The assay used to measure amphotericin B in the serum after administration of AmBisome does not
10 distinguish amphotericin B that is complexed with the phospholipids of AmBisome from amphotericin B
11 that is uncomplexed. The pharmacokinetic profile of amphotericin B after administration of AmBisome
12 is based upon total serum concentrations of amphotericin B. The pharmacokinetic profile of
13 amphotericin B was determined in febrile neutropenic cancer and bone marrow transplant patients who
14 received 1-2 hour infusions of 1.0 to 5.0 mg/kg/day AmBisome for 3 to 20 days.

15 The pharmacokinetics of amphotericin B after administration of AmBisome are nonlinear such
16 that there is a greater than proportional increase in serum concentrations with an increase in dose from
17 1.0 to 5.0 mg/kg/day. The pharmacokinetic parameters of total amphotericin B (mean \pm SD) after the
18 first dose and at steady state are shown in the table below.

19

Pharmacokinetic Parameters of AmBisome

Dose (mg/kg/day):	1.0		2.5		5.0	
Day	1 n = 8	Last n = 7	1 n = 7	Last n = 7	1 n = 12	Last n = 9
Parameters						
C _{max} (mcg/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 (mcg•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 _{ss} (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

1

2 **Distribution**

3 Based on total amphotericin B concentrations measured within a dosing interval (24 hours) after
 4 administration of AmBisome, the mean half-life was 7-10 hours. However, based on total amphotericin
 5 B concentration measured up to 49 days after dosing of AmBisome, the mean half-life was 100-153
 6 hours. The long terminal elimination half-life is probably a slow redistribution from tissues. Steady state
 7 concentrations were generally achieved within 4 days of dosing.

8 Although variable, mean trough concentrations of amphotericin B remained relatively constant with
 9 repeated administration of the same dose over the range of 1.0 to 5.0 mg/kg/day, indicating no
 10 significant drug accumulation in the serum.

11

12 **Metabolism**

13 The metabolic pathways of amphotericin B after administration of AmBisome are not known.

14

15 **Excretion**

16 The mean clearance at steady state was independent of dose. The excretion of amphotericin B after
 17 administration of AmBisome has not been studied.

18

1 **Pharmacokinetics in Special Populations**

2 **Renal Impairment**

3 The effect of renal impairment on the disposition of amphotericin B after administration of AmBisome
4 has not been studied. However, AmBisome has been successfully administered to patients with pre-
5 existing renal impairment (see **DESCRIPTION OF CLINICAL STUDIES**).

6
7 **Hepatic Impairment**

8 The effect of hepatic impairment on the disposition of amphotericin B after administration of AmBisome
9 is not known.

10
11 **Pediatric and Elderly Patients**

12 The pharmacokinetics of amphotericin B after administration of AmBisome in pediatric and elderly
13 patients have not been studied; however, AmBisome has been used in pediatric and elderly patients
14 (see **DESCRIPTION OF CLINICAL STUDIES**).

15
16 **Gender and Ethnicity**

17 The effect of gender or ethnicity on the pharmacokinetics of amphotericin B after administration of
18 AmBisome is not known.

19
20 **INDICATIONS AND USAGE:**

21 AmBisome is indicated for the following:

- 22
- Empirical therapy for presumed fungal infection in febrile, neutropenic patients.
 - Treatment of Cryptococcal Meningitis in HIV infected patients (see **DESCRIPTION OF CLINICAL STUDIES**).
 - Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections (see above for the treatment of Cryptococcal Meningitis) refractory to amphotericin B
- 26

1 deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use
2 of amphotericin B deoxycholate.

- 3 • Treatment of visceral leishmaniasis. In immunocompromised patients with visceral leishmaniasis
4 treated with AmBisome, relapse rates were high following initial clearance of parasites (see

5 **DESCRIPTION OF CLINICAL STUDIES).**

6 See **DOSAGE AND ADMINISTRATION** for recommended doses by indication.

7
8 **DESCRIPTION OF CLINICAL STUDIES:**

9 Eleven clinical studies supporting the efficacy and safety of AmBisome were conducted. This clinical
10 program included both controlled and uncontrolled studies. These studies, which involved 2171
11 patients, included patients with confirmed systemic mycoses, empirical therapy, and visceral
12 leishmaniasis.

13 Nineteen hundred and forty-six episodes were evaluable for efficacy, of which 1280 (302
14 pediatric and 978 adults) were treated with AmBisome.

15 Three controlled empirical therapy trials compared the efficacy and safety of AmBisome to
16 amphotericin B. One of these studies was conducted in a pediatric population, one in adults, and a third
17 in patients aged 2 years or more. In addition, a controlled empirical therapy trial comparing the safety
18 of AmBisome to Abelcet® (amphotericin B lipid complex) was conducted on patients aged 2 years or
19 more.

20 One controlled trial compared the efficacy and safety of AmBisome to amphotericin B in HIV
21 patients with cryptococcal meningitis.

22
23 One compassionate use study enrolled patients who had failed amphotericin B deoxycholate therapy or
24 who were unable to receive amphotericin B deoxycholate because of renal insufficiency.

25
26 **Empirical Therapy in Febrile Neutropenic Patients**

27 Study 94-0-002, a randomized, double-blind, comparative multi-center trial, evaluated the efficacy of
28 AmBisome (1.5-6.0 mg/kg/day) compared with amphotericin B deoxycholate (0.3-1.2 mg/kg/day) in

1 the empirical treatment of 687 adult and pediatric neutropenic patients who were febrile despite having
 2 received at least 96 hours of broad spectrum antibacterial therapy. Therapeutic success required (a)
 3 resolution of fever during the neutropenic period, (b) absence of an emergent fungal infection, (c) patient
 4 survival for at least 7 days post therapy, (d) no discontinuation of therapy due to toxicity or lack of
 5 efficacy, and (e) resolution of any study-entry fungal infection.

6 The overall therapeutic success rates for AmBisome and the amphotericin B deoxycholate were
 7 equivalent. Results are summarized in the following table. Note: The categories presented below are
 8 not mutually exclusive.

9
**Empirical Therapy in Febrile Neutropenic Patients:
 Randomized, Double-Blind Study in 687 Patients**

	AmBisome	Amphotericin B
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 (87.7%)
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%)

10 * 8 and 10 patients, respectively, were treated as failures due to premature discontinuation alone.

11
 12 This therapeutic equivalence had no apparent relationship to the use of prestudy antifungal
 13 prophylaxis or concomitant granulocytic colony stimulating factors.

14 The incidence of mycologically confirmed and clinically diagnosed, emergent fungal infections
 15 are presented in the following table. AmBisome and amphotericin B were found to be equivalent with
 16 respect to the total number of emergent fungal infections.

**Empirical Therapy in Febrile Neutropenic Patients:
 Emergent Fungal Infections**

	AmBisome	Amphotericin B

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%)

1

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

4 Study 97-0-034, a randomized, double-blind, comparative multi-center trial, evaluated the
5 safety of AmBisome (3.0 and 5.0 mg/kg/day) compared with amphotericin B lipid complex (5
6 mg/kg/day) in the empirical treatment of 202 adult and 42 pediatric neutropenic patients. One hundred
7 and sixty-six patients received AmBisome (85 patients received 3 mg/kg/day and 81 received 5
8 mg/kg/day) and 78 patients received amphotericin B lipid complex. The study patients were febrile
9 despite having received at least 72 hours of broad spectrum antibacterial therapy. The primary endpoint
10 of this study was safety. The study was not designed to draw statistically meaningful conclusions related
11 to comparative efficacy, and in fact, Abelcet is not labeled for this indication.

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

19

20 **Treatment of Cryptococcal Meningitis in HIV Infected Patients.**

21 Study 94-0-013, a randomized, double-blind, comparative multi-center trial, evaluated the efficacy of
22 AmBisome at doses (3.0 and 6.0 mg/kg/day) compared with amphotericin B deoxycholate (0.7
23 mg/kg/day) for the treatment of cryptococcal meningitis in 266 adult and one pediatric HIV positive

1 patients (the pediatric patient received amphotericin B deoxycholate). Of the 267 treated patients, 86
 2 received AmBisome 3 mg/kg/day, 94 received 6 mg/kg/day and 87 received amphotericin B
 3 deoxycholate; cryptococcal meningitis was documented by a positive CSF culture at baseline in 73, 85
 4 and 76 patients, respectively. Patients received study drug once daily for an induction period of 11 to
 5 21 days. Following induction, all patients were switched to oral fluconazole at 400 mg/day for adults
 6 and 200 mg/day for patients less than 13 years of age to complete 10 weeks of protocol-directed
 7 therapy. For mycologically evaluable patients, defined as all randomized patients who received at least
 8 one dose of study drug, had a positive baseline CSF culture, and had at least one follow-up culture,
 9 success was evaluated at week 2 (i.e., 14 ± 4 days), and was defined as CSF culture conversion.
 10 Success rates at 2 weeks for AmBisome and amphotericin B deoxycholate are summarized in the
 11 following table:

12
 13 **Success Rates at 2 weeks (CSF Culture Conversion) Study 94-0-013**

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B 0.7 mg/kg
Success at Week 2	35/60 (58.3%) 97.5% CI ¹ = -9.4%, +31.0%	36/75 (48%) 97.5% CI ¹ = -18.8%, +19.8%	29/61 (47.5 %)

14
 15 ¹ 97.5% Confidence Interval for the difference between AmBisome and amphotericin B success rates. A negative
 16 value is in favor of amphotericin B. A positive value is in favor of AmBisome.

17
 18 Success at 10 weeks was defined as clinical success at week 10 plus CSF culture conversion at or
 19 prior to week 10. Success rates at 10 weeks in patients with positive baseline culture for cryptococcus
 20 species are summarized in the following table and show that the efficacy of AmBisome 6 mg/kg/day
 21 approximates the efficacy of the amphotericin B deoxycholate regimen. These data do not support the
 22 conclusion that AmBisome 3 mg/kg/day is comparable in efficacy to amphotericin B deoxycholate. The
 23 table also presents 10-week survival rates for patients treated in this study.

24

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. 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 was defined as CSF culture conversion. Success rates at 2 weeks for AmBisome and amphotericin B deoxycholate are summarized in the following table:

Success Rates at 2 weeks (CSF Culture Conversion) Study 94-0-013

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B 0.7 mg/kg
Success at Week 2	35	36	29

[Redacted]

† Ninety percent 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.

[Redacted]

Success Rates at week 10, Study 94-0-013

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B 0.7 mg/kg
Success at week 10	27	42	40

† Ninety percent Confidence Interval for the difference between AmBisome and amphotericin B rates. A negative value is in favor of amphotericin B. A positive value is in favor of AmBisome.

There was insufficient information available to conclude that AmBisome given at 3 mg/kg/day is as effective as amphotericin B at 0.7 mg/kg/day.

Success Rates and Survival Rates at week 10, Study 94-0-013
(see text for definitions)

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B 0.7 mg/kg
Success in patients with documented cryptococcal meningitis	27/73 (37%) 97.5% CI ¹ = -33.7%, +2.4%	42/85 (49%) 97.5% CI ¹ = -20.9%, 14.5%	40/76 (53%)
Survival rates	74/86 (86%) 97.5% CI ¹ = -13.8%, +8.9%	85/94 (90%) 97.5% CI ¹ = -8.3%, +12.2%	77/87 (89%)

¹ 97.5% Confidence Interval for the difference between AmBisome and amphotericin B rates. A negative value is in favor of amphotericin B. A positive value is in favor of AmBisome.

The incidence of infusion-related, cardiovascular and renal adverse events was lower in patients receiving AmBisome compared to amphotericin B deoxycholate (see ADVERSE REACTIONS section for details), therefore, the risks and benefits (advantages and disadvantages) of the different amphotericin B formulations should be taken into consideration when selecting a patient treatment regimen.

Treatment of Patients with *Aspergillus* Species, *Candida* Species and/or *Cryptococcus* Species Infections Refractory to Amphotericin B Deoxycholate, or in Patients Where Renal Impairment or Unacceptable Toxicity Precludes the Use of Amphotericin B Deoxycholate

AmBisome was evaluated in a compassionate use study in hospitalized patients with systemic fungal infections. These patients either had fungal infections refractory to amphotericin B deoxycholate, were intolerant to the use of amphotericin B deoxycholate, or had pre-existing renal insufficiency. Patient recruitment involved 140 infectious episodes in 133 patients, with 53 episodes evaluable for mycological response and 91 episodes evaluable for clinical outcome. Clinical success and mycological eradication occurred in some patients with documented aspergillosis, candidiasis, and cryptococcosis.

1 **Treatment of Visceral Leishmaniasis**

2 AmBisome was studied in patients with visceral leishmaniasis who were infected in the Mediterranean
3 basin with documented or presumed *Leishmania infantum*. Clinical studies have not provided
4 conclusive data regarding efficacy against *L. donovani* or *L. chagasi*.

5 AmBisome achieved high rates of acute parasite clearance in immunocompetent patients when
6 total doses of 12-30 mg/kg were administered. Most of these immunocompetent patients remained
7 relapse-free during follow-up periods of 6 months or longer. While acute parasite clearance was
8 achieved in most of the immunocompromised patients who received total doses of 30-40 mg/kg, the
9 majority of these patients were observed to relapse in the 6 months following the completion of therapy.
10 Of the 21 immunocompromised patients studied, 17 were coinfecting with HIV; approximately half of
11 the HIV infected patients had AIDS. The following table presents a comparison of efficacy rates among
12 immunocompetent and immunocompromised patients infected in the Mediterranean basin who had no
13 prior treatment or remote prior treatment for visceral leishmaniasis. Efficacy is expressed as both acute
14 parasite clearance at the end of therapy (EOT) and as overall success (clearance with no relapse) during
15 the follow-up period (F/U) of greater than 6 months for immunocompetent and immunocompromised
16 patients:

17

AmBisome Efficacy in Visceral Leishmaniasis

Immunocompetent Patients			
No. of Patients		Parasite (%) Clearance at EOT	Overall Success (%) at F/U
87		86/87 (98.9)	83/86 (96.5)
Immunocompromised Patients			
Regimen	Total Dose	Parasite (%) Clearance at EOT	Overall Success (%) at F/U
100 mg/day X 21 days	29.0-38.9 mg/kg	10/10 (100)	2/10 (20.0)
4 mg/kg/day, days 1-5, and 10, 17, 24, 31, 38	40 mg/kg	8/9 (88.9)	0/7 (0.0)
TOTAL		18/19 (94.7)	2/17 (11.8)

1 When followed for 6 months or more after treatment, the overall success rate among
2 immunocompetent patients was 96.5% and the overall success rate among immunocompromised
3 patients was 11.8% due to relapse in the majority of patients. While case reports have suggested there
4 may be a role for long-term therapy to prevent relapses in HIV coinfecting patients (Lopez-Dupla, et al.
5 *J Antimicrob Chemother* 1993; 32: 657-659), there are no data to date documenting the efficacy or
6 safety of repeat courses of AmBisome or of maintenance therapy with this drug among
7 immunocompromised patients.

8

9 **CONTRAINDICATIONS:**

10 AmBisome is contraindicated in those patients who have demonstrated or have known hypersensitivity
11 to amphotericin B deoxycholate or any other constituents of the product unless, in the opinion of the
12 treating physician, the benefit of therapy outweighs the risk.

13

14 **WARNINGS:**

15 Anaphylaxis has been reported with amphotericin B deoxycholate and other amphotericin B-containing
16 drugs, including AmBisome. If a severe anaphylactic reaction occurs, the infusion should be
17 immediately discontinued and the patient should not receive further infusions of AmBisome.

18

19 **PRECAUTIONS:**

20 **General**

21 As with any amphotericin B-containing product the drug should be administered by medically trained
22 personnel. During the initial dosing period, patients should be under close clinical observation.
23 AmBisome has been shown to be significantly less toxic than amphotericin B deoxycholate; however,
24 adverse events may still occur.

25

26 **Laboratory Tests**

27 Patient management should include laboratory evaluation of renal, hepatic and hematopoietic function,
28 and serum electrolytes (particularly magnesium and potassium).

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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 and corticotropin (ACTH): Concurrent use of corticosteroids and ACTH 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 may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion.

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.

1 *Other nephrotoxic medications:* Concurrent use of amphotericin B and other nephrotoxic medications
2 may enhance the potential for drug-induced renal toxicity. Intensive monitoring of renal function is
3 recommended in patients requiring any combination of nephrotoxic medications.

4
5 *Skeletal muscle relaxants:* Amphotericin B-induced hypokalemia may enhance the curariform effect
6 of skeletal muscle relaxants (e.g. tubocurarine) due to hypokalemia. When administered concomitantly,
7 serum potassium levels should be closely monitored.

8

9 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

10 No long term studies in animals have been performed to evaluate carcinogenic potential of AmBisome.
11 AmBisome has not been tested to determine its mutagenic potential. A Segment I Reproductive Study
12 in rats found an abnormal estrous cycle (prolonged diestrus) and decreased number of corpora lutea in
13 the high dose groups (10 and 15 mg/kg, doses equivalent to human doses of 1.6 and 2.4 mg/kg based
14 on body surface area considerations). AmBisome did not affect fertility or days to copulation. There
15 were no effects on male reproductive function.

16

17 **Pregnancy Category B**

18 There have been no adequate and well-controlled studies of AmBisome in pregnant women. Systemic
19 fungal infections have been successfully treated in pregnant women with amphotericin B deoxycholate,
20 but the number of cases reported has been small.

21 Segment II studies in both rats and rabbits have concluded that AmBisome had no teratogenic
22 potential in these species. In rats, the maternal non-toxic dose of AmBisome was estimated to be 5
23 mg/kg (equivalent to 0.16 to 0.8 times the recommended human clinical dose range of 1 to 5 mg/kg)
24 and in rabbits, 3 mg/kg (equivalent to 0.2 to 1 times the recommended human clinical dose range),
25 based on body surface area correction. Rabbits receiving the higher doses, (equivalent to 0.5 to 2 times
26 the recommended human dose) of AmBisome experienced a higher rate of spontaneous abortions than
27 did the control groups. AmBisome should only be used during pregnancy if the possible benefits to be
28 derived outweigh the potential risks involved.

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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 breast-fed 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.

Pediatric Use

Pediatric patients, age 1 month to 16 years, with presumed fungal infection (empirical therapy), confirmed systemic fungal infections or with visceral leishmaniasis have been successfully 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 have not been established.

(See **DESCRIPTION OF CLINICAL STUDIES - Empirical Therapy in Febrile Neutropenic Patients** and **DOSAGE AND ADMINISTRATION**.)

Elderly Patients

Experience with AmBisome in the elderly (65 years or older) comprised 72 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.

ADVERSE REACTIONS:

The following adverse events are based on the experience of 592 adult patients (295 treated with AmBisome and 297 treated with amphotericin B deoxycholate) and 95 pediatric patients (48 treated with AmBisome and 47 treated with amphotericin B deoxycholate) in Study 94-0-002, a randomized

1 double-blind, multi-center study in febrile, neutropenic patients. AmBisome and amphotericin B were
2 infused over two hours.

3 The incidence of common adverse events (incidence of 10% or greater) occurring with
4 AmBisome compared to amphotericin B deoxycholate, regardless of relationship to study drug, is
5 shown in the following table:

Empirical Therapy Study 94-0-002
Common 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 react.	18.4	18.6
Chills	47.5	75.9
Infection	11.1	9.3
Pain	14.0	12.8
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
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	14.0	14.0

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

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

12 The following adverse events are based on the experience of 244 patients (202 adult and 42
13 pediatric patients) of whom 85 patients were treated with AmBisome 3 mg/kg, 81 patients were treated
14 with AmBisome 5 mg/kg and 78 patients treated with amphotericin B lipid complex 5 mg/kg in Study
15 97-0-034, a randomized double-blind, multi-center study in febrile, neutropenic patients. AmBisome
16 and amphotericin B lipid complex were infused over two hours. The incidence of adverse events
17 occurring in more than 10% of subjects in one or more arms regardless of relationship to study drug are
18 summarized in the following table:

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**Empirical Therapy Study 97-0-034
Common Adverse Events**

Adverse Event by Body System	AmBisome	AmBisome	Amphotericin B Lipid Complex
	3/mg/kg/day n=85 %	5/mg/kg/day n=81 %	5/mg/kg/day n=78 %
Body as a Whole			
Abdominal pain	12.9	9.9	11.5
Asthenia	8.2	6.2	11.5
Chills/rigors	40.0	48.1	89.7
Sepsis	12.9	7.4	11.5
Transfusion reaction	10.6	8.6	5.1
Cardiovascular System			
Chest pain	8.2	11.1	6.4
Hypertension	10.6	19.8	23.1
Hypotension	10.6	7.4	19.2
Tachycardia	9.4	18.5	23.1
Digestive System			
Diarrhea	15.3	17.3	14.1
Nausea	25.9	29.6	37.2
Vomiting	22.4	25.9	30.8
Metabolic and Nutritional Disorders			
Alkaline phosphatase increased	7.1	8.6	12.8
Bilirubinemia	16.5	11.1	11.5
BUN increased	20.0	18.5	28.2
Creatinine increased	20.0	18.5	48.7
Edema	12.9	12.3	12.8
Hyperglycemia	8.2	8.6	14.1
Hypervolemia	8.2	11.1	14.1
Hypocalcemia	10.6	4.9	5.1
Hypokalemia	37.6	43.2	39.7
Hypomagnesemia	15.3	25.9	15.4
Liver function tests abnormal	10.6	7.4	11.5
Nervous System			
Anxiety	10.6	7.4	9.0
Confusion	12.9	8.6	3.8
Headache	9.4	17.3	10.3
Respiratory System			
Dyspnea	17.6	22.2	23.1
Epistaxis	10.6	8.6	14.1
Hypoxia	7.1	6.2	20.5
Lung disorder	14.1	13.6	15.4
Skin and Appendages			
Rash	23.5	22.2	14.1

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4

1 The following adverse events are based on the experience of 267 patients (266 adult patients
2 and 1 pediatric patient) of whom 86 patients were treated with AmBisome 3 mg/kg, 94 patients were
3 treated with AmBisome 6 mg/kg and 87 patients treated with amphotericin B deoxycholate 0.7 mg/kg
4 in Study 94-0-013 a randomized, double-blind, comparative multi-center trial, in the treatment of
5 cryptococcal meningitis in HIV positive patients. The incidence of adverse events occurring in more
6 than 10% of subjects in one or more arms regardless of relationship to study drug are summarized in the
7 following table:

Cryptococcal Meningitis Therapy Study 94-0-013
Common Adverse Events

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

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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 deoxycholate-treated patients.

The incidence of infusion related reactions on Day 1 in pediatric and adult patients is summarized in the following table:

Incidence of Day 1 Infusion Related Reactions (IRR) By Patient Age

	Pediatric Patients (≤ 16 years of age)		Adult Patients (> 16 years of age)	
	AmBisome	Amphotericin B	AmBisome	Amphotericin B
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%)

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

1 Cardiorespiratory events, except for vasodilatation (flushing), during all study drug infusions
2 were more frequent in amphotericin B-treated patients as summarized in the following table:

Incidence of Infusion Related Cardiorespiratory Events

Event	AmBisome n=343	Amphotericin B 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%)

3
4 The percentage of patients who received drugs either for the treatment or prevention of infusion
5 related reactions (e.g., acetaminophen, diphenhydramine, meperidine and hydrocortisone) was lower in
6 AmBisome-treated patients compared with amphotericin B deoxycholate-treated patients.

7 In the empirical therapy study 97-0-034, on Day 1, where no premedication was administered,
8 the overall incidence of infusion related events of chills/rigors was significantly lower for patients
9 administered AmBisome compared with amphotericin B lipid complex. Fever, chills/rigors and hypoxia
10 were significantly lower for each AmBisome group compared with the amphotericin B lipid complex
11 group. The infusion related event hypoxia was reported for 11.5% of amphotericin B lipid complex-
12 treated patients compared with 0% of patients administered 3 mg/kg per day AmBisome and 1.2% of
13 patients treated with 5 mg/kg per day AmBisome.

**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(Day1)	16 (18.8%)	19 (23.5%)	35 (21.1%)	62 (79.5%)
Patients with other notable reactions:				
Fever ($\geq 1.0^{\circ}\text{C}$ increase in temperature)	20 (23.5%)	16 (19.8%)	36 (21.7%)	45 (57.7%)
Nausea	9 (10.6%)	7 (8.6%)	16 (9.6%)	9 (11.5%)
Vomiting	5 (5.9%)	5 (6.2%)	10 (6.0%)	11 (14.1%)
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 premedications 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 deoxycholate as initial therapy for cryptococcal meningitis, premedications to prevent infusion related reactions were permitted. AmBisome treated patients had a lower incidence of fever, chill/rigors and respiratory adverse events as summarized in the following table:

Incidence of Infusion-Related Reactions Study 94-0-013			
	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B
Total number of patients receiving at least one dose of study drug	86	94	87
Patients with fever increase of $>1^{\circ}\text{C}$	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%)

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

7 **Toxicity and Discontinuation of Dosing**

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

12 In empirical therapy study 97-0-034, a greater proportion of patients in the amphotericin B lipid
13 complex group discontinued the study drug due to an adverse event than in the AmBisome groups.

15 **Less Common Adverse Events**

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

20 *Body as a Whole* - abdomen enlarged, allergic reaction, cellulitis, cell mediated immunological reaction,
21 face edema, graft versus host disease, malaise, neck pain, and procedural complication.

23 *Cardiovascular System*- arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, cardiomegaly,
24 hemorrhage, postural hypotension, valvular heart disease, vascular disorder, and vasodilatation
25 (flushing).

27 *Digestive System* - anorexia, constipation, dry mouth/nose, dyspepsia, dysphagia, eructation, fecal
28 incontinence, flatulence, hemorrhoids, gum/oral hemorrhage, hematemesis, hepatocellular damage,

1 hepatomegaly, liver function test abnormal, ileus, mucositis, rectal disorder, stomatitis, ulcerative
2 stomatitis, and veno-occlusive liver disease.

3
4 *Hemic & Lymphatic System* - anemia, coagulation disorder, ecchymosis, fluid overload, petechia,
5 prothrombin decreased, prothrombin increased, and thrombocytopenia.

6
7 *Metabolic & Nutritional Disorders* - acidosis, amylase increased, hyperchloremia, hyperkalemia,
8 hypermagnesemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactate
9 dehydrogenase increased, nonprotein nitrogen (NPN) increased, and respiratory alkalosis.

10
11 *Musculoskeletal System* - arthralgia, bone pain, dystonia, myalgia, and rigors.

12
13 *Nervous System* - agitation, coma, convulsion, cough, depression, dysesthesia, dizziness, hallucinations,
14 nervousness, paresthesia, somnolence, thinking abnormality, and tremor.

15
16 *Respiratory System* - asthma, atelectasis, hemoptysis, hiccup, hyperventilation, influenza-like
17 symptoms, lung edema, pharyngitis, pneumonia, respiratory insufficiency, respiratory failure, and
18 sinusitis.

19
20 *Skin & Appendages* - alopecia, dry skin, herpes simplex, injection site inflammation, maculopapular
21 rash, purpura, skin discoloration, skin disorder, skin ulcer, urticaria, and vesiculobullous rash.

22
23 *Special Senses* - conjunctivitis, dry eyes, and eye hemorrhage.

24
25 *Urogenital System* - abnormal renal function, acute kidney failure, acute renal failure, dysuria, kidney
26 failure, toxic nephropathy, urinary incontinence, and vaginal hemorrhage.

27 The following infrequent adverse experiences have been reported in post-marketing
28 surveillance, in addition to those mentioned above: angioedema, erythema, urticaria,
29 cyanosis/hypoventilation, pulmonary edema, agranulocytosis, hemorrhagic cystitis.

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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. The frequency and magnitude of hepatic test abnormalities were similar in the AmBisome and amphotericin B groups. 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.

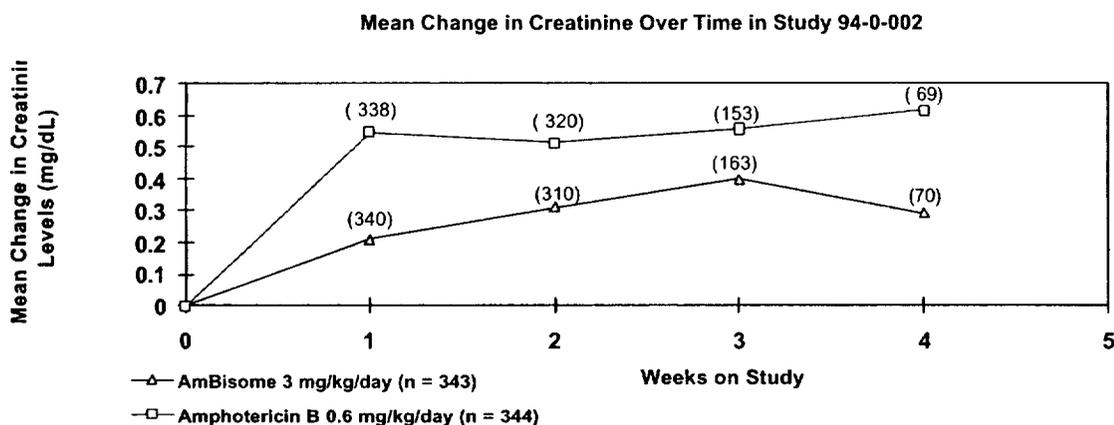
Incidence of nephrotoxicity, mean peak serum creatinine concentration, mean change from baseline in serum creatinine, and, incidence of hypokalemia in the double-blind randomized study were lower in the AmBisome group as summarized in the following table:

Study 94-0-002 Laboratory Evidence of Nephrotoxicity

	AmBisome	Amphotericin B
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%)

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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 the following figure:



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In empirical therapy study 97-0-034, the incidence of nephrotoxicity as measured by increases of serum creatinine from baseline was significantly lower for patients administered AmBisome (individual dose groups and combined) compared with amphotericin B lipid complex.

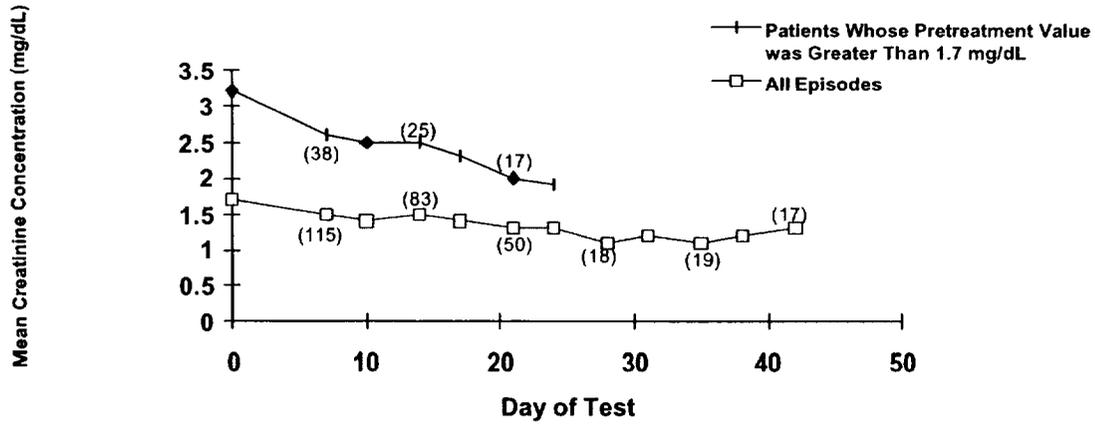
**Incidence of Nephrotoxicity
Empirical Therapy Study 97-0-034**

	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 creatinine value	12 (14.1%)	12 (14.8%)	24 (14.5%)	33 (42.3%)

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The following graph shows the average serum creatinine concentrations in the compassionate use study and shows that there is a drop from pretreatment concentrations for all patients, especially those with elevated (greater than 1.7 mg/dL) pretreatment creatinine concentrations.

Mean Creatinine Concentrations Over Time



- 1
- 2 The incidence of nephrotoxicity in Study 94-0-013, comparative trial in cryptococcal meningitis was
- 3 lower in the AmBisome groups as shown in the following table:

1

Laboratory Evidence of Nephrotoxicity Study 94-0-013			
	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B
Total number of patients receiving at least one dose of study drug	86	94	87
Number with Nephrotoxicity (%)			
1.5X baseline serum creatinine	30 (35%)	44 (47%)	52 (60%)
2 X baseline serum creatinine	12 (14%)	20 (21%)	29 (33%)

2

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4 **OVERDOSAGE:**

5 The toxicity of AmBisome due to overdose has not been defined. Repeated daily doses up to
6 10 mg/kg in pediatric patients and 15 mg/kg in adult patients have been administered in clinical trials
7 with no reported dose-related toxicity.

8 Management - If overdosage should occur, cease administration immediately. Symptomatic
9 supportive measures should be instituted. Particular attention should be given to monitoring renal
10 function.

11

12 **DOSAGE AND ADMINISTRATION:**

13 AmBisome should be administered by intravenous infusion, using a controlled infusion device, over a
14 period of approximately 120 minutes.

15

16 An in-line membrane filter may be used for the intravenous infusion of AmBisome; provided
17 **THE MEAN PORE DIAMETER OF THE FILTER IS NOT LESS THAN 1.0 MICRON.**

18

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

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2 Infusion time may be reduced to approximately 60 minutes in patients in whom the treatment is well-
3 tolerated. If the patient experiences discomfort during infusion, the duration of infusion may be
4 increased.

5 The recommended initial dose of AmBisome for each indication for adult and pediatric patients
6 is as follows:

Indication	Dose (mg/kg/day)
Empirical therapy	3.0
Systemic fungal infections: <i>Aspergillus</i> <i>Candida</i> <i>Cryptococcus</i>	3.0 - 5.0
Cryptococcal meningitis in HIV infected patients (see DESCRIPTION OF CLINICAL STUDIES)	6.0

7
8 Dosing and rate of infusion should be individualized to the needs of the specific patient to ensure
9 maximum efficacy while minimizing systemic toxicities or adverse events.

10 Doses recommended for visceral leishmaniasis are presented below:

Visceral Leishmaniasis	Dose (mg/kg/day)
Immunocompetent patients	3.0 (days 1-5) and 3.0 on days 14, 21
Immunocompromised patients	4.0 (days 1-5) and 4.0 on days 10, 17, 24, 31, 38

11
12 For immunocompetent patients who do not achieve parasitic clearance with the
13 recommended dose, a repeat course of therapy may be useful.

1 **For immunocompromised patients** who do not clear parasites or who experience relapses,
2 expert advice regarding further treatment is recommended. For additional information see

3 **DESCRIPTION OF CLINICAL STUDIES.**

4
5 **Directions for Reconstitution, Filtration and Dilution**

6 **Read This Entire Section Carefully Before Beginning Reconstitution**

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

9
10 **Reconstitution**

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

13 **CAUTION:DO NOT RECONSTITUTE WITH SALINE OR ADD SALINE TO THE**
14 **RECONSTITUTED CONCENTRATION, OR MIX WITH OTHER DRUGS.** The use of
15 any solution other than those recommended, or the presence of a bacteriostatic agent in the solution,
16 may cause precipitation of AmBisome.

- 17 2. **Immediately after the addition of water, SHAKE THE VIAL VIGOROUSLY** for 30
18 seconds to completely disperse the AmBisome. AmBisome forms a yellow, translucent suspension.
19 Visually inspect the vial for particulate matter and continue shaking until completely dispersed.

20
21 **Filtration and Dilution**

- 22 3. Calculate the amount of reconstituted (4 mg/mL) AmBisome to be further diluted.
23 4. Withdraw this amount of reconstituted AmBisome into a sterile syringe.
24 5. Attach the 5-micron filter, provided, to the syringe. Inject the syringe contents through the filter, into
25 the appropriate amount of 5% Dextrose Injection. (Use only one filter per vial of AmBisome.)
26 6. AmBisome must be diluted with 5% Dextrose Injection to a final concentration of 1.0 to 2.0 mg/mL
27 prior to administration. Lower concentrations (0.2 to 0.5 mg/mL) may be appropriate for infants

1 and small children to provide sufficient volume for infusion. **DISCARD PARTIALLY USED**
2 **VIALS.**

3

4 **STORAGE OF AMBISOME:**

5 Unopened vials of lyophilized material must be stored under refrigeration at 2°-8° C (36°-46° F).

6

7 **Storage of Reconstituted Product Concentrate**

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

10

11 **Storage of Diluted Product**

12 Injection of AmBisome should commence within 6 hours of dilution with 5% Dextrose Injection.

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

18

19 **HOW SUPPLIED:**

20 AmBisome for Injection is available as single 50 mg vial cartons and in packs of ten individual vial
21 cartons (NDC 0469-3051-30).

22 Each carton contains one pre-packaged, disposable sterile 5 micron filter.

23

24 **Rx only**

25

26 **Manufactured for:**

27 Fujisawa Healthcare, Inc.

28 Deerfield, IL 60015-2548

1 **by:**

2 Gilead Sciences, Inc.

3 San Dimas, CA 91773

4

5 AmBisome is a registered trademark of Gilead Sciences, Inc.

6 Abelcet® is a registered trademark of The Liposome Company, Inc.

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