

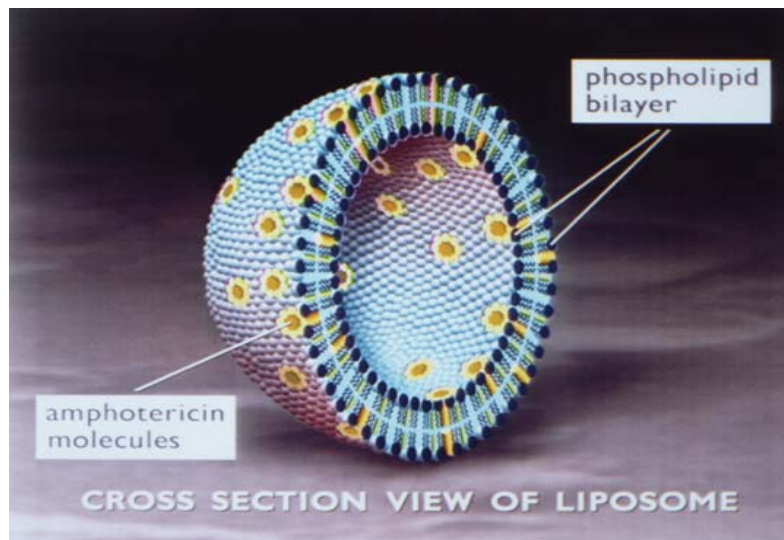
1 **AmBisome®**
2 **(amphotericin B) liposome for injection**
3
4

5 Revised: October 2008
6

7 **DESCRIPTION**

8 AmBisome for Injection is a sterile, non-pyrogenic lyophilized product for
9 intravenous infusion. Each vial contains 50 mg of amphotericin B, USP,
10 intercalated into a liposomal membrane consisting of approximately 213 mg
11 hydrogenated soy phosphatidylcholine; 52 mg cholesterol, NF; 84 mg
12 distearoylphosphatidylglycerol; 0.64 mg alpha tocopherol, USP; together with
13 900 mg sucrose, NF; and 27 mg disodium succinate hexahydrate as buffer.
14 Following reconstitution with Sterile Water for Injection, USP, the resulting pH of
15 the suspension is between 5-6.
16

17 AmBisome is a true single bilayer liposomal drug delivery system. Liposomes
18 are closed, spherical vesicles created by mixing specific proportions of
19 amphophilic substances such as phospholipids and cholesterol so that they
20 arrange themselves into multiple concentric bilayer membranes when hydrated
21 in aqueous solutions. Single bilayer liposomes are then formed by
22 microemulsification of multilamellar vesicles using a homogenizer. AmBisome
23 consists of these unilamellar bilayer liposomes with amphotericin B intercalated
24 within the membrane. Due to the nature and quantity of amphophilic substances
25 used, and the lipophilic moiety in the amphotericin B molecule, the drug is an
26 integral part of the overall structure of the AmBisome liposomes. AmBisome
27 contains true liposomes that are less than 100 nm in diameter. A schematic
28 depiction of the liposome is presented below.
29



72 been established and results of such studies do not necessarily correlate with
73 clinical outcome.

74

75 AmBisome is active in animal models against *Aspergillus fumigatus*, *Candida*
76 *albicans*, *Candida krusei*, *Candida lusitanae*, *Cryptococcus neoformans*,
77 *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*,
78 *Paracoccidioides brasiliensis*, *Leishmania donovani*, and *Leishmania infantum*.
79 The administration of AmBisome in these animal models demonstrated
80 prolonged survival of infected animals, reduction of microorganisms from target
81 organs, or a decrease in lung weight.

82

83 **Drug Resistance**

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

90

91 **CLINICAL PHARMACOLOGY**

92 **Pharmacokinetics**

93 The assay used to measure amphotericin B in the serum after administration of
94 AmBisome does not distinguish amphotericin B that is complexed with the
95 phospholipids of AmBisome from amphotericin B that is uncomplexed. The
96 pharmacokinetic profile of amphotericin B after administration of AmBisome is
97 based upon total serum concentrations of amphotericin B. The
98 pharmacokinetic profile of amphotericin B was determined in febrile neutropenic
99 cancer and bone marrow transplant patients who received 1-2 hour infusions of
100 1 to 5 mg/kg/day AmBisome for 3 to 20 days.

101 The pharmacokinetics of amphotericin B after administration of AmBisome are
102 nonlinear such that there is a greater than proportional increase in serum
103 concentrations with an increase in dose from 1 to 5 mg/kg/day. The
104 pharmacokinetic parameters of total amphotericin B (mean \pm SD) after the first
105 dose and at steady state are shown in the table below.

106

Pharmacokinetic Parameters of AmBisome

Dose (mg/kg/day):	1		2.5		5	
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	83 ± 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 ± 2.1	8.1 ± 2.3	6.3 ± 2	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

107

108

Distribution

109

Based on total amphotericin B concentrations measured 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 a slow redistribution from tissues. Steady state concentrations were generally achieved within 4 days of dosing.

111

112

113

114

115

116

Although variable, mean trough concentrations of amphotericin B remained relatively constant with repeated administration of the same dose over the range of 1 to 5 mg/kg/day, indicating no significant drug accumulation in the serum.

117

118

119

120

121

Metabolism

122

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

123

124

125

Excretion

126

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

127

128

129

Pharmacokinetics in Special Populations

130

Renal Impairment

131

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

132

133

134

135

136

Hepatic Impairment

137

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

138

139

140 ***Pediatric and Elderly Patients***

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

145

146 ***Gender and Ethnicity***

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

149

150 **INDICATIONS AND USAGE**

151 AmBisome is indicated for the following:

152

153 • Empirical therapy for presumed fungal infection in febrile, neutropenic
154 patients.

155 • Treatment of Cryptococcal Meningitis in HIV infected patients (see
156 **DESCRIPTION OF CLINICAL STUDIES**).

157 • Treatment of patients with *Aspergillus* species, *Candida* species and/or
158 *Cryptococcus* species infections (see above for the treatment of
159 Cryptococcal Meningitis) refractory to amphotericin B deoxycholate, or in
160 patients where renal impairment or unacceptable toxicity precludes the use
161 of amphotericin B deoxycholate.

162 • Treatment of visceral leishmaniasis. In immunocompromised patients with
163 visceral leishmaniasis treated with AmBisome, relapse rates were high
164 following initial clearance of parasites (see **DESCRIPTION OF CLINICAL**
165 **STUDIES**).

166

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

168

169 **DESCRIPTION OF CLINICAL STUDIES**

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

174

175 Nineteen hundred and forty-six episodes were evaluable for efficacy, of which
176 1280 (302 pediatric and 978 adults) were treated with AmBisome.

177

178 Three controlled empirical therapy trials compared the efficacy and safety of
179 AmBisome to amphotericin B. One of these studies was conducted in a
180 pediatric population, one in adults, and a third in patients aged 2 years or more.
181 In addition, a controlled empirical therapy trial comparing the safety of
182 AmBisome to Abelcet® (amphotericin B lipid complex) was conducted in
183 patients aged 2 years or more.

184

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

187

188 One compassionate use study enrolled patients who had failed amphotericin B
189 deoxycholate therapy or who were unable to receive amphotericin B
190 deoxycholate because of renal insufficiency.

191

192 **Empirical Therapy in Febrile Neutropenic Patients**

193 Study 94-0-002, a randomized, double-blind, comparative multi-center trial,
194 evaluated the efficacy of AmBisome (1.5-6 mg/kg/day) compared with
195 amphotericin B deoxycholate (0.3-1.2 mg/kg/day) in the empirical treatment of
196 687 adult and pediatric neutropenic patients who were febrile despite having
197 received at least 96 hours of broad spectrum antibacterial therapy. Therapeutic
198 success required (a) resolution of fever during the neutropenic period, (b)
199 absence of an emergent fungal infection, (c) patient survival for at least 7 days
200 post therapy, (d) no discontinuation of therapy due to toxicity or lack of efficacy,
201 and (e) resolution of any study-entry fungal infection.

202

203 The overall therapeutic success rates for AmBisome and the amphotericin B
204 deoxycholate were equivalent. Results are summarized in the following table.

205 Note: The categories presented below are not mutually exclusive.

206

**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%)	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%)

207 * 8 and 10 patients, respectively, were treated as failures due to premature discontinuation
208 alone.

209

210 This therapeutic equivalence had no apparent relationship to the use of
211 prestudy antifungal prophylaxis or concomitant granulocytic colony stimulating
212 factors.

213

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

218

**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%)

219

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

222

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

233

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

243

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

245 Study 94-0-013, a randomized, double-blind, comparative multi-center trial,
246 evaluated the efficacy of AmBisome at doses (3 and 6 mg/kg/day) compared
247 with amphotericin B deoxycholate (0.7 mg/kg/day) for the treatment of
248 cryptococcal meningitis in 266 adult and one pediatric HIV positive patients (the
249 pediatric patient received amphotericin B deoxycholate). Of the 267 treated
250 patients, 86 received AmBisome 3 mg/kg/day, 94 received 6 mg/kg/day and 87
251 received amphotericin B deoxycholate; cryptococcal meningitis was
252 documented by a positive CSF culture at baseline in 73, 85 and 76 patients,
253 respectively. Patients received study drug once daily for an induction period of
254 11 to 21 days. Following induction, all patients were switched to oral
255 fluconazole at 400 mg/day for adults and 200 mg/day for patients less than 13

256 years of age to complete 10 weeks of protocol-directed therapy. For
 257 mycologically evaluable patients, defined as all randomized patients who
 258 received at least one dose of study drug, had a positive baseline CSF culture,
 259 and had at least one follow-up culture, success was evaluated at week 2 (i.e.,
 260 14 ± 4 days), and was defined as CSF culture conversion. Success rates at 2
 261 weeks for AmBisome and amphotericin B deoxycholate are summarized in the
 262 following table:

263 **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%	36/75 (48%) 97.5% CI ¹ = -18.8%, +19.8%	29/61 (47.5 %)

265
 266 ¹ 97.5% Confidence Interval for the difference between AmBisome and amphotericin B
 267 success rates. A negative value is in favor of amphotericin B. A positive value is in
 268 favor of AmBisome.

269
 270 Success at 10 weeks was defined as clinical success at week 10 plus CSF
 271 culture conversion at or prior to week 10. Success rates at 10 weeks in patients
 272 with positive baseline culture for cryptococcus species are summarized in the
 273 following table and show that the efficacy of AmBisome 6 mg/kg/day
 274 approximates the efficacy of the amphotericin B deoxycholate regimen. These
 275 data do not support the conclusion that AmBisome 3 mg/kg/day is comparable
 276 in efficacy to amphotericin B deoxycholate. The table also presents 10-week
 277 survival rates for patients treated in this study.

278
 279
 280 **Success Rates and Survival Rates at week 10, Study 94-0-013**
 281 (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%)

282
 283 ¹ 97.5% Confidence Interval for the difference between AmBisome and amphotericin B
 284 rates. A negative value is in favor of amphotericin B. A positive value is in favor of
 285 AmBisome.

286
 287 The incidence of infusion-related, cardiovascular and renal adverse events was
 288 lower in patients receiving AmBisome compared to amphotericin B
 289 deoxycholate (see **ADVERSE REACTIONS** section for details), therefore, the
 290 risks and benefits (advantages and disadvantages) of the different amphotericin

291 B formulations should be taken into consideration when selecting a patient
292 treatment regimen.

293

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

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

306

307 **Treatment of Visceral Leishmaniasis**

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

312

313 AmBisome achieved high rates of acute parasite clearance in
314 immunocompetent patients when total doses of 12-30 mg/kg were
315 administered. Most of these immunocompetent patients remained relapse-free
316 during follow-up periods of 6 months or longer. While acute parasite clearance
317 was achieved in most of the immunocompromised patients who received total
318 doses of 30-40 mg/kg, the majority of these patients were observed to relapse
319 in the 6 months following the completion of therapy. Of the 21
320 immunocompromised patients studied, 17 were coinfecting with HIV;
321 approximately half of the HIV infected patients had AIDS. The following table
322 presents a comparison of efficacy rates among immunocompetent and
323 immunocompromised patients infected in the Mediterranean basin who had no
324 prior treatment or remote prior treatment for visceral leishmaniasis. Efficacy is
325 expressed as both acute parasite clearance at the end of therapy (EOT) and as
326 overall success (clearance with no relapse) during the follow-up period (F/U) of
327 greater than 6 months for immunocompetent and immunocompromised
328 patients:

329

330

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 (%)	Overall Success (%) at

		Clearance at EOT	F/U
100 mg/day X 21 days	29-38.9 mg/kg	10/10 (100)	2/10 (20)
4 mg/kg/day, days 1-5, and 10, 17, 24, 31, 38	40 mg/kg	8/9 (88.9)	0/7 (0)
TOTAL		18/19 (94.7)	2/17 (11.8)

331

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

340

341 **CONTRAINDICATIONS**

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

346

347 **WARNINGS**

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

352

353 **PRECAUTIONS**

354 **General**

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

360

361 **Laboratory Tests**

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

365

366 **Drug Interactions**

367 No formal clinical studies of drug interactions have been conducted with
368 AmBisome. However, the following drugs are known to interact with
369 amphotericin B and may interact with AmBisome:

370

371 ***Antineoplastic Agents***

372 Concurrent use of antineoplastic agents may enhance the potential for renal
373 toxicity, bronchospasm, and hypotension. Antineoplastic agents should be
374 given concomitantly with caution.

375

376 ***Corticosteroids and Corticotropin (ACTH)***

377 Concurrent use of corticosteroids and ACTH may potentiate hypokalemia which
378 could predispose the patient to cardiac dysfunction. If used concomitantly,
379 serum electrolytes and cardiac function should be closely monitored.

380

381 ***Digitalis Glycosides***

382 Concurrent use may induce hypokalemia and may potentiate digitalis toxicity.
383 When administered concomitantly, serum potassium levels should be closely
384 monitored.

385

386 ***Flucytosine***

387 Concurrent use of flucytosine may increase the toxicity of flucytosine by
388 possibly increasing its cellular uptake and/or impairing its renal excretion.

389

390 ***Azoles (e.g. ketoconazole, miconazole, clotrimazole, fluconazole, etc.)***

391 *In vitro* and *in vivo* animal studies of the combination of amphotericin B and
392 imidazoles suggest that imidazoles may induce fungal resistance to
393 amphotericin B. Combination therapy should be administered with caution,
394 especially in immunocompromised patients.

395

396 ***Leukocyte Transfusions***

397 Acute pulmonary toxicity has been reported in patients simultaneously receiving
398 intravenous amphotericin B and leukocyte transfusions.

399

400 ***Other Nephrotoxic Medications***

401 Concurrent use of amphotericin B and other nephrotoxic medications may
402 enhance the potential for drug-induced renal toxicity. Intensive monitoring of
403 renal function is recommended in patients requiring any combination of
404 nephrotoxic medications.

405

406 ***Skeletal Muscle Relaxants***

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

411

412 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

421

422 **Pregnancy Category B**

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

427

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

438

439 **Nursing Mothers**

440 Many drugs are excreted in human milk. However, it is not known whether
441 AmBisome is excreted in human milk. Due to the potential for serious adverse
442 reactions in breast-fed infants, a decision should be made whether to
443 discontinue nursing or whether to discontinue the drug, taking into account the
444 importance of the drug to the mother.

445

446 **Pediatric Use**

447 Pediatric patients, age 1 month to 16 years, with presumed fungal infection
448 (empirical therapy), confirmed systemic fungal infections or with visceral
449 leishmaniasis have been successfully treated with AmBisome. In studies which
450 included 302 pediatric patients administered AmBisome, there was no evidence
451 of any differences in efficacy or safety of AmBisome compared to adults. Since
452 pediatric patients have received AmBisome at doses comparable to those used
453 in adults on a per kilogram body weight basis, no dosage adjustment is required
454 in this population. Safety and effectiveness in pediatric patients below the age
455 of one month have not been established. (See **DESCRIPTION OF CLINICAL
456 STUDIES - Empirical Therapy in Febrile Neutropenic Patients** and
457 **DOSAGE AND ADMINISTRATION.**)

458

459 **Elderly Patients**

460 Experience with AmBisome in the elderly (65 years or older) comprised 72
461 patients. It has not been necessary to alter the dose of AmBisome for this
462 population. As with most other drugs, elderly patients receiving AmBisome
463 should be carefully monitored.

464

465 **ADVERSE REACTIONS**

466 The following adverse events are based on the experience of 592 adult patients
467 (295 treated with AmBisome and 297 treated with amphotericin B deoxycholate)
468 and 95 pediatric patients (48 treated with AmBisome and 47 treated with
469 amphotericin B deoxycholate) in Study 94-0-002, a randomized double-blind,
470 multi-center study in febrile, neutropenic patients. AmBisome and amphotericin
471 B were infused over two hours.

472

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

476

477

478

**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	7.3
Blood product transfusion react.	18.4	18.6
Chills	47.5	75.9
Infection	11.1	9.3
Pain	14	12.8
Sepsis	14	11.3
Cardiovascular System		
Chest pain	12	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
AST (SGOT) increased	12.8	12.8

Bilirubinemia	18.1	19.2
BUN increased	21	31.1
Creatinine increased	22.4	42.2
Edema	14.3	14.8
Hyperglycemia	23	27.9
Hypernatremia	4.1	11
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
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	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
Skin and Appendages		
Pruritus	10.8	10.2
Rash	24.8	24.4
Sweating	7	10.8
Urogenital System		
Hematuria	14	14

479

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

484

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

494

495 The following adverse events are based on the experience of 244 patients (202
496 adult and 42 pediatric patients) of whom 85 patients were treated with
497 AmBisome 3 mg/kg, 81 patients were treated with AmBisome 5 mg/kg and 78
498 patients treated with amphotericin B lipid complex 5 mg/kg in Study 97-0-034, a

499 randomized double-blind, multi-center study in febrile, neutropenic patients.
500 AmBisome and amphotericin B lipid complex were infused over two hours. The
501 incidence of adverse events occurring in more than 10% of subjects in one or
502 more arms regardless of relationship to study drug are summarized in the
503 following table:
504

505
506

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

Adverse Event by Body System	AmBisome 3/mg/kg/day n=85 %	AmBisome 5/mg/kg/day n=81 %	Amphotericin B Lipid Complex 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	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	18.5	28.2
Creatinine increased	20	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
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

507
508
509
510

The following adverse events are based on the experience of 267 patients (266 adult patients and 1 pediatric patient) of whom 86 patients were treated with

511 AmBisome 3 mg/kg, 94 patients were treated with AmBisome 6 mg/kg and 87
 512 patients treated with amphotericin B deoxycholate 0.7 mg/kg in Study 94-0-013
 513 a randomized, double-blind, comparative multi-center trial, in the treatment of
 514 cryptococcal meningitis in HIV positive patients. The incidence of adverse
 515 events occurring in more than 10% of subjects in one or more arms regardless
 516 of relationship to study drug are summarized in the following table:
 517

**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	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	9.6	11.5
Constipation	15.1	14.9	20.7
Diarrhea	10.5	16	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	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	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	8.5	10.3
Insomnia	22.1	17	20.7
Respiratory System			
Cough Increased	8.1	2.1	10.3
Skin and Appendages			
Rash	4.7	11.7	4.6

518
 519
 520
 521
 522

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

523 administered prior to the first dose of study drug (Day 1). AmBisome-treated
 524 patients had a lower incidence of infusion related fever (17% versus 44%),
 525 chills/rigors (18% versus 54%) and vomiting (6% versus 8%) on Day 1 as
 526 compared to amphotericin B deoxycholate-treated patients.

527
 528 The incidence of infusion related reactions on Day 1 in pediatric and adult
 529 patients is summarized in the following table:
 530

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%)

531 †Day 1 body temperature increased above the temperature taken within 1 hour prior to
 532 infusion (preinfusion temperature) or above the lowest infusion value (no preinfusion
 533 temperature recorded).
 534

535 Cardiorespiratory events, except for vasodilatation (flushing), during all study
 536 drug infusions were more frequent in amphotericin B-treated patients as
 537 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%)

538
 539 The percentage of patients who received drugs either for the treatment or
 540 prevention of infusion related reactions (e.g., acetaminophen, diphenhydramine,
 541 meperidine and hydrocortisone) was lower in AmBisome-treated patients
 542 compared with amphotericin B deoxycholate-treated patients.

543

544 In the empirical therapy study 97-0-034, on Day 1, where no premedication was
545 administered, the overall incidence of infusion related events of chills/rigors was
546 significantly lower for patients administered AmBisome compared with
547 amphotericin B lipid complex. Fever, chills/rigors and hypoxia were significantly
548 lower for each AmBisome group compared with the amphotericin B lipid
549 complex group. The infusion related event hypoxia was reported for 11.5% of
550 amphotericin B lipid complex-treated patients compared with 0% of patients
551 administered 3 mg/kg per day AmBisome and 1.2% of patients treated with 5
552 mg/kg per day AmBisome.

553
554
555

**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%)	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%)	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%)

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

559
560 Patients were not administered premedications to prevent infusion related reactions prior to the
561 Day 1 study drug infusion.

562
563 In Study 94-0-013, a randomized double-blind multicenter trial comparing
564 AmBisome and amphotericin B deoxycholate as initial therapy for cryptococcal
565 meningitis, premedications to prevent infusion related reactions were permitted.
566 AmBisome treated patients had a lower incidence of fever, chill/rigors and
567 respiratory adverse events as summarized in the following table:
568

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%)

569
570 There have been a few reports of flushing, back pain with or without chest
571 tightness, and chest pain associated with AmBisome administration; on
572 occasion this has been severe. Where these symptoms were noted, the
573 reaction developed within a few minutes after the start of infusion and
574 disappeared rapidly when the infusion was stopped. The symptoms do not

575 occur with every dose and usually do not recur on subsequent administrations
576 when the infusion rate is slowed.

577

578 **Toxicity and Discontinuation of Dosing**

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

584

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

588

589 **Less Common Adverse Events**

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

593

594 ***Body as a Whole***

595 Abdomen enlarged, allergic reaction, cellulitis, cell mediated immunological
596 reaction, face edema, graft versus host disease, malaise, neck pain, and
597 procedural complication.

598

599 ***Cardiovascular System***

600 Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, cardiomegaly,
601 hemorrhage, postural hypotension, valvular heart disease, vascular disorder,
602 and vasodilatation (flushing).

603

604 ***Digestive System***

605 Anorexia, constipation, dry mouth/nose, dyspepsia, dysphagia, eructation, fecal
606 incontinence, flatulence, hemorrhoids, gum/oral hemorrhage, hematemesis,
607 hepatocellular damage, hepatomegaly, liver function test abnormal, ileus,
608 mucositis, rectal disorder, stomatitis, ulcerative stomatitis, and veno-occlusive
609 liver disease.

610

611 ***Hemic & Lymphatic System***

612 Anemia, coagulation disorder, ecchymosis, fluid overload, petechia,
613 prothrombin decreased, prothrombin increased, and thrombocytopenia.

614

615 ***Metabolic & Nutritional Disorders***

616 Acidosis, amylase increased, hyperchloremia, hyperkalemia,
617 hypermagnesemia, hyperphosphatemia, hyponatremia, hypophosphatemia,
618 hypoproteinemia, lactate dehydrogenase increased, nonprotein nitrogen (NPN)
619 increased, and respiratory alkalosis.

620

621 ***Musculoskeletal System***

622 Arthralgia, bone pain, dystonia, myalgia, and rigors.

623

624 ***Nervous System***

625 Agitation, coma, convulsion, cough, depression, dysesthesia, dizziness,
626 hallucinations, nervousness, paresthesia, somnolence, thinking abnormality,
627 and tremor.

628

629 ***Respiratory System***

630 Asthma, atelectasis, hemoptysis, hiccup, hyperventilation, influenza-like
631 symptoms, lung edema, pharyngitis, pneumonia, respiratory insufficiency,
632 respiratory failure, and sinusitis.

633

634 ***Skin & Appendages***

635 Alopecia, dry skin, herpes simplex, injection site inflammation, maculopapular
636 rash, purpura, skin discoloration, skin disorder, skin ulcer, urticaria, and
637 vesiculobullous rash.

638

639 ***Special Senses***

640 Conjunctivitis, dry eyes, and eye hemorrhage.

641

642 ***Urogenital System***

643 Abnormal renal function, acute kidney failure, acute renal failure, dysuria,
644 kidney failure, toxic nephropathy, urinary incontinence, and vaginal
645 hemorrhage.

646

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

651

652 ***Clinical Laboratory Values***

653 The effect of AmBisome on renal and hepatic function and on serum
654 electrolytes was assessed from laboratory values measured repeatedly in Study
655 94-0-002. The frequency and magnitude of hepatic test abnormalities were
656 similar in the AmBisome and amphotericin B groups. Nephrotoxicity was
657 defined as creatinine values increasing 100% or more over pretreatment levels
658 in pediatric patients, and creatinine values increasing 100% or more over
659 pretreatment levels in adult patients provided the peak creatinine concentration
660 was >1.2 mg/dL. Hypokalemia was defined as potassium levels ≤ 2.5 mmol/L
661 any time during treatment.

662

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

667

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%)

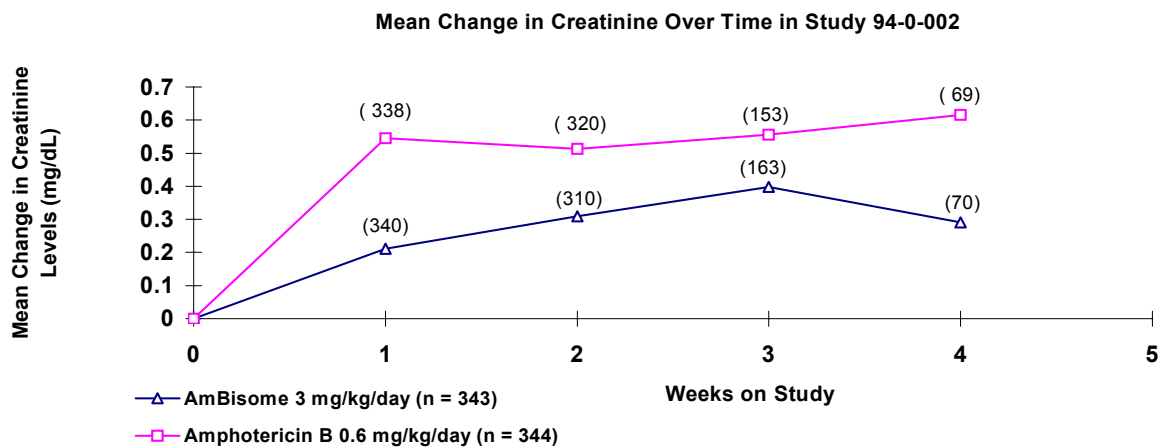
668

669

670

671

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:



672

673

674

675

676

677

678

679

680

681

682

683

684

685

686

687

688

689

690

691

692

693

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%)

694

695

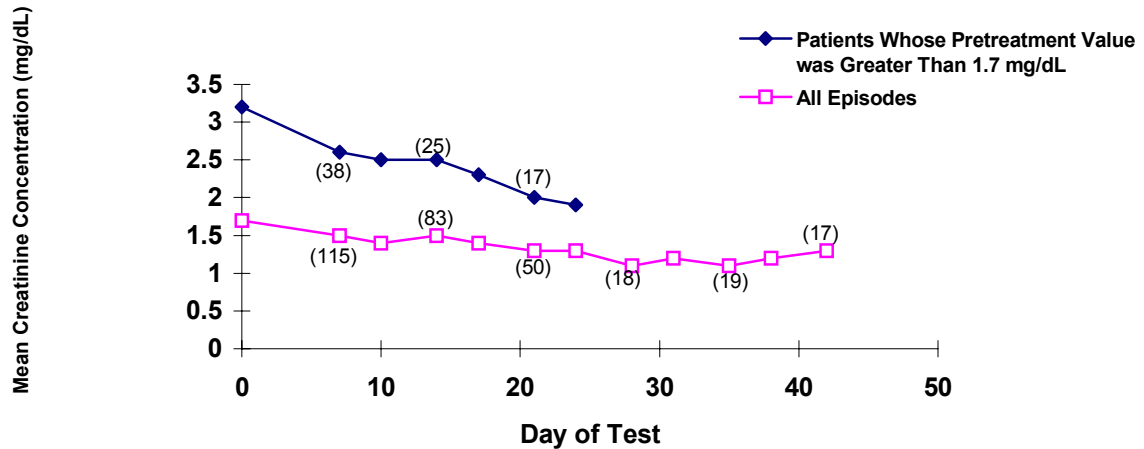
696

697

698

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



699

700

701

702

703

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

704

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%)

705

706 **OVERDOSAGE**

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

710

711 **Management**

712 If overdosage should occur, cease administration immediately. Symptomatic
713 supportive measures should be instituted. Particular attention should be given
714 to monitoring renal function. Hemodialysis or peritoneal dialysis do not appear
715 to significantly affect the elimination of AmBisome.

716

717 **DOSAGE AND ADMINISTRATION**

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

720

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

724

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

728

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

732

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

Indication	Dose (mg/kg/day)
Empirical therapy	3
Systemic fungal infections: <i>Aspergillus</i> <i>Candida</i> <i>Cryptococcus</i>	3-5
Cryptococcal meningitis in HIV infected patients (see DESCRIPTION OF CLINICAL STUDIES)	6

735

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

739

740 Doses recommended for visceral leishmaniasis are presented below:

741

Visceral Leishmaniasis	Dose (mg/kg/day)
Immunocompetent patients	3 (days 1-5) and 3 on days 14, 21
Immunocompromised patients	4 (days 1-5) and 4 on days 10, 17, 24, 31, 38

742

743 **For immunocompetent patients** who do not achieve parasitic clearance with
744 the recommended dose, a repeat course of therapy may be useful.

745

746 **For immunocompromised patients** who do not clear parasites or who
747 experience relapses, expert advice regarding further treatment is
748 recommended. For additional information see **DESCRIPTION OF CLINICAL**
749 **STUDIES**.

750

751 **Directions for Reconstitution, Filtration and Dilution**

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

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

756

757 **Reconstitution**

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

760

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

765 2. **Immediately after the addition of water, SHAKE THE VIAL**
766 **VIGOROUSLY** for 30 seconds to completely disperse the AmBisome.
767 AmBisome forms a yellow, translucent suspension. Visually inspect the vial
768 for particulate matter and continue shaking until completely dispersed.
769

770 ***Filtration and Dilution***

771 3. Calculate the amount of reconstituted (4 mg/mL) AmBisome to be further
772 diluted.
773 4. Withdraw this amount of reconstituted AmBisome into a sterile syringe.
774 5. Attach the 5-micron filter, provided, to the syringe. Inject the syringe
775 contents through the filter, into the appropriate amount of 5% Dextrose
776 Injection. (Use only one filter per vial of AmBisome.)
777 6. AmBisome must be diluted with 5% Dextrose Injection to a final
778 concentration of 1 to 2 mg/mL prior to administration. Lower concentrations
779 (0.2 to 0.5 mg/mL) may be appropriate for infants and small children to
780 provide sufficient volume for infusion. **DISCARD PARTIALLY USED**
781 **VIALS.**
782

783 **STORAGE OF AMBISOME**

784 Unopened vials of lyophilized material are to be stored at temperatures up to
785 25° C (77° F).
786

787 **Storage of Reconstituted Product Concentrate**

788 The reconstituted product concentrate may be stored for up to 24 hours at 2°-8°
789 C (36°-46° F) following reconstitution with Sterile Water for Injection, USP. Do
790 not freeze.
791

792 **Storage of Diluted Product**

793 Injection of AmBisome should commence within 6 hours of dilution with 5%
794 Dextrose Injection.
795

796 As with all parenteral drug products, the reconstituted AmBisome should be
797 inspected visually for particulate matter and discoloration prior to administration,
798 whenever solution and container permit. Do not use material if there is any
799 evidence of precipitation or foreign matter. Aseptic technique must be strictly
800 observed in all handling since no preservative or bacteriostatic agent is present
801 in AmBisome or in the materials specified for reconstitution and dilution.
802

803 **HOW SUPPLIED**

804 AmBisome for Injection is available as single cartons (equivalent to 50mg
805 amphotericin B) and in packs of ten individual vial cartons
806 (NDC 0469-3051-30).
807

808 Each carton contains one pre-packaged, disposable sterile 5 micron filter.
809

810 **Rx only**

811

812 **Marketed by:**

813 Astellas Pharma US, Inc.

814 Deerfield, IL 60015-2548

815

816 **Manufactured by:**

817 Gilead Sciences, Inc.

818 San Dimas, CA 91773

819

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

821 Abelcet[®] is a registered trademark of The Liposome Company, Inc.

822

823 Revised: October 2008

824

825