IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED,	)	
Plaintiff,	)	
v.	)	Case No. 06-438-GMS
ABRAXIS BIOSCIENCE, INC.,	)	
Defendant.	)	

DECLARATION OF LISA A. CHIARINI IN SUPPORT OF PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S MOTION FOR CLARIFICATION AND/OR PARTIAL RECONSIDERATION OF ORDER CONSTRUING THE TERMS OF U.S. PATENT NO. 5,834,025

I, Lisa A. Chiarini, hereby declare under penalty of perjury pursuant to 28 U.S.C. Section 1746 as follows:

1. I am a member in good standing of the New York State Bar, am admitted to this Court *pro hac vice* in this matter, and am an associate with the law firm of Baker Botts, L.L.P., counsel of record for Elan Pharma International Limited in the above captioned action. I submit this Declaration based upon personal knowledge. If called upon as a witness, I could, and would, competently testify to the truth of each statement herein.

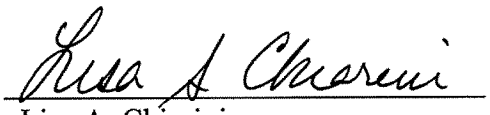
2. Attached hereto as Exhibit 1 is a true and correct copy of the Abraxane® Prescribing Information package insert, May 2007 Version.

3. Attached hereto as Exhibit 2 is a true and correct copy of the AmBisome® Prescribing Information package insert, Revised July 2005 Version.

I declare and affirm under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

FURTHER DECLARANT SAYETH NOT.

Executed this 31th day of August, 2007 in New York, New York.



Lisa A. Chiarini

EXHIBIT 1

Version: May 2007

Rx Only

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

(Patient Information Enclosed)

WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

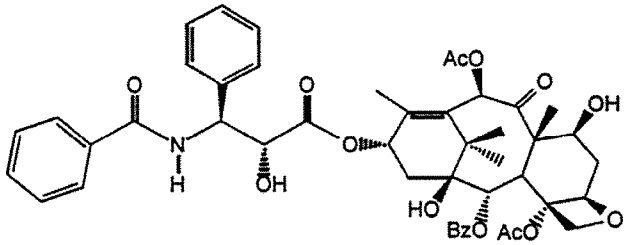
Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE® is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Human Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline

representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE® were independent of the duration of administration. At the recommended ABRAXANE clinical dose, 260 mg/m^2, the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m^2. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over 3 hours. The clearance of ABRAXANE was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of ABRAXANE was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3 -*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3 -*p*-hydroxypaclitaxel and 6α, 3 -*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole,

verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4 (see **PRECAUTIONS: Drug Interactions**). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE® has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Metastatic Breast Carcinoma:

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies- In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30 minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3 week intervals. Objective responses were observed in both studies.

Randomized Comparative Study- This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-

nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE® treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 1. There was no statistically significant difference in overall survival between the two study arms.

Table 1: Efficacy Results from Randomized Trial

		ABRAXANE 260 mg/m²	**Paclitaxel Injection 175 mg/m²**
Reconciled Target Lesion Response Rate (primary endpoint) [a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	P-value [b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

[c] Prior therapy included an anthracycline unless clinically contraindicated.

INDICATION

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.

WARNINGS

Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm^3. Frequent monitoring of blood counts should be instituted during ABRAXANE treatment. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

The use of ABRAXANE has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy – Teratogenic Effects: Pregnancy Category D: ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal

malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE®. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

Use in Males: Men should be advised to not father a child while receiving treatment with ABRAXANE (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** for discussion of effects of ABRAXANE exposure on male fertility and embryonic viability).

Albumin (Human): ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

Drug Interactions: No drug interaction studies have been conducted with ABRAXANE.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see **CLINICAL PHARMACOLOGY**).

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Hematology: ABRAXANE® therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE and ADMINISTRATION**).

Nervous System: Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE (see **DOSAGE and ADMINISTRATION**).

Injection Site Reaction: Injection site reactions occur infrequently with ABRAXANE and were mild in the randomized clinical trial. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m^2 basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12

mg/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m^2 and dogs administered 175 mg/m^2 (see **WARNINGS**).

Pregnancy: Teratogenic Effects: Pregnancy Category D: (See **WARNINGS** section).

Nursing Mothers: It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE® therapy.

Pediatric Use: The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric use: Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

Information for Patients: (See **Patient Information Leaflet**).

ADVERSE REACTIONS:

The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE® or paclitaxel injection for the treatment of metastatic breast cancer.

Table 2: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE® 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4

Table 2: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule, Continued

	Percent of Patients	
	ABRAXANE® 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade.
[b] ABRAXANE dose in mg/m^2/duration in minutes.
[c] paclitaxel injection dose in mg/m^2/duration in hours.
[d] paclitaxel injection pts received premedication.
[e] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[f] Severe events are defined as at least grade 3 toxicity.
[g] During study drug dosing.

Myelosuppression and sensory neuropathy were dose related.

Adverse Event Experiences by Body System: Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE® in the randomized controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hematologic: Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2.

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb <8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs): In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of

ABRAXANE® in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

During postmarketing surveillance, rare occurrences of severe hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

Cardiovascular: Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory: Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE. Rare reports of interstitial pneumonia, lung fibrosis, and

pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE with concurrent radiotherapy.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE®. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial.

Cranial nerve palsies have been reported during postmarketing surveillance of ABRAXANE. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred

vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia: Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE® administration, and resolved within a few days.

Hepatic: Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Renal: Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions have occurred infrequently with ABRAXANE and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia: Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE® in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events: Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment: skin abnormalities related to radiation recall as well as reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation. As part of the continuing surveillance of ABRAXANE, skin reactions including generalized or maculo-papular rash, erythema, and pruritis have been observed. Additionally, there have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae. Because these events have been reported during

clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Accidental Exposure: No reports of accidental exposure to ABRAXANE® have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE

There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSAGE AND ADMINISTRATION

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment: The appropriate dose of ABRAXANE for patients with bilirubin greater than 1.5 mg/dL is not known.

Dose Reduction: Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

Preparation and Administration Precautions: ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in

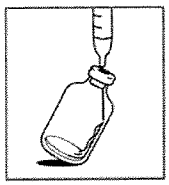
handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE® contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see **PRECAUTIONS: Injection Site Reaction**).

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE.

Preparation for Intravenous Administration: ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.



3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE® into an empty, sterile IV bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability: Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25° C) and lighting conditions for up to 8 hours.

HOW SUPPLIED

Product No. 103450

NDC No. 68817-134-50 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

Storage: Store the vials in original cartons at 20° C to 25° C (68° F to 77°F). Retain in the original package to protect from bright light.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

U.S. Patent Numbers: 5,439,686; 5,498,421; 6,096,331; 6,506,405; 6,537,579; 6,749,868; 6,753,006

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Publication No. 83-2621. For sale by the Superintendent of Documents, US Government NIH Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure Recommendations for Handling Cytotoxic Agents. Available from Louis R Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of

Pharmacy and Allied Health Sciences. 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*, 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians*, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*, 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK-PRACTICE GUIDELINES.) *Am J Health-Syst Pharm*, 1996; 53:1669-1686.
8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

Issued: May 2007

ABRAXIS
ONCOLOGY
A Division of Abraxis BioScience, Inc.
Los Angeles, CA 90049

PATIENT INFORMATION

ABRAXANE® for Injectable Suspension

[generic name = (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)]

WHAT IS ABRAXANE?

ABRAXANE is a prescription cancer medicine. It is injected into a vein and it is used to treat advanced breast cancer.

WHAT IS CANCER?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood. A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

HOW DOES ABRAXANE WORK?

ABRAXANE is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. ABRAXANE may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by ABRAXANE causing some of the side effects. (see **WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?** below).

WHO SHOULD NOT TAKE ABRAXANE?

ABRAXANE should not be given to patients with dangerously low white blood cell counts.

HOW IS ABRAXANE® GIVEN?

ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes.

WHAT PREMEDICATION IS REQUIRED WITH ABRAXANE?

While reactions can occur to any medication, severe allergic reactions to ABRAXANE are uncommon and premedication is not required. However, you should make your doctor aware of any allergies you may have so he/she can determine the course of action required.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?

Most patients taking ABRAXANE will experience side effects, although it is not always possible to tell whether such effects are caused by ABRAXANE, another medicine they may be taking, or the cancer itself. Important side effects are described below; however, some patients may experience other side effects that are less common. *Report any unusual symptoms to your doctor.*

Important side effects observed in studies of patients taking ABRAXANE were as follows:

Hair Loss: Complete hair loss, or alopecia, almost always occurs with ABRAXANE. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your ABRAXANE treatment.*

Infections Due to Low White Blood Cell Count: Among the body's defenses against bacterial infections are white blood cells. Between your ABRAXANE treatment cycles, you will often have blood tests to check your white blood cell counts. ABRAXANE usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4°F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

Numbness, Tingling, or Burning in the Hands and/or Feet (Neuropathy): These symptoms occur often with ABRAXANE® and usually get better or go away without medication within three weeks of interrupting treatment. Be sure to tell your doctor about any numbness, tingling or burning that you have in your hands or feet so that he/she can decide the best approach for relief of your symptoms. Sometimes it is necessary to interrupt treatment with ABRAXANE until these symptoms improve. After improvement, treatment can be restarted at a lower dose.

Fatigue and Weakness: ABRAXANE may cause asthenia, fatigue, weakness, lethargy and malaise. These side effects are usually self-limited and do not require dose modification or interruption.

Low Red Blood Cell Count: Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following ABRAXANE treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following ABRAXANE treatment.

Mouth or Lip Sores (Mucositis): Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the ABRAXANE treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

Joint and Muscle Pain: You may get joint and muscle pain a few days after your ABRAXANE treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

Stomach Upset and Diarrhea: Some patients experience nausea, vomiting, and/or diarrhea following ABRAXANE use. If you experience nausea or stomach upset, tell your doctor because medicines can be given that almost always reduce or eliminate these symptoms.

Diarrhea will usually disappear without treatment; however, *if you experience severe abdominal or stomach area pain and/or severe diarrhea, tell your doctor right away.*

Heart and Blood Vessel (Cardiovascular) Effects: ABRAXANE® may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. You should notify your doctor if you have a history of heart disease.

Irritation at the Injection Site: ABRAXANE may cause irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the I.V. (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with ABRAXANE, it is important to talk with your doctor about other possible side effects.

CAN I TAKE ABRAXANE IF I AM PREGNANT OR NURSING A BABY?

ABRAXANE could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with ABRAXANE. *Tell your doctor if you become pregnant or plan to become pregnant while taking ABRAXANE.*

Men should be advised not to father a child while receiving treatment with ABRAXANE.

Because studies have shown the active agent (paclitaxel) in ABRAXANE to be present in the breast milk of animals receiving the active agent, it may be present in human breast milk as well. Therefore, nursing a baby while taking ABRAXANE is NOT recommended. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE therapy.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about ABRAXANE®. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about ABRAXANE, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

ABRAXIS
ONCOLOGY

A Division of Abraxis BioScience, Inc.
Los Angeles, CA 90049

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.
Based on: ABRAXANE Package Insert issued: May 2007
Revised: May 2007

EXHIBIT 2

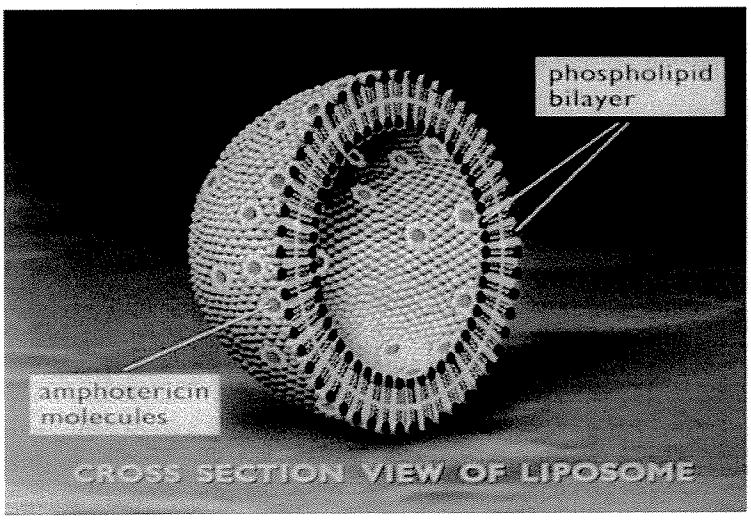
AmBisome®
(amphotericin B) liposome for injection

Revised: July 2005

DESCRIPTION

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

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

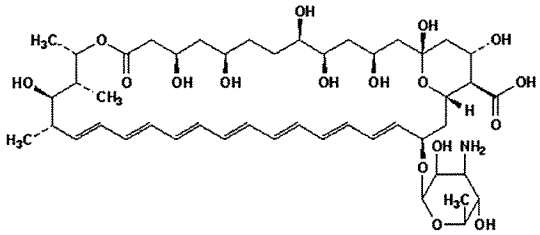


Note: Liposomal encapsulation or incorporation into a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated drug or non-lipid associated drug. In addition, different liposomal or lipid-complex products with a common active ingredient may vary from 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.

The structure of amphotericin B is shown below:



MICROBIOLOGY

Mechanism of Action

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

Activity In Vitro and In Vivo

Am**B**isome has shown *in vitro* activity comparable to amphotericin B against the following organisms: *Aspergillus* species *(A. fumigatus, A. flavus), Candida* species *(C. albicans, C. krusei, C. lusitaniae, C. parapsilosis, C. tropicalis), Cryptococcus neoformans,* and *Blastomyces dermatitidis.* However, standardized techniques for susceptibility testing of antifungal agents have not

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

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

Drug Resistance

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

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

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
$t_{½}$(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 ± 0.1	0.10 ± 0.07
Cl (mL/hr/kg)	39 ± 22	17 ± 6	51 ± 44	22 ± 15	21 ± 14	11 ± 6

Distribution

Based on total amphotericin B concentrations measured within a dosing interval (24 hours) after administration of Am**B**isome, the mean half-life was 7-10 hours. However, based on total amphotericin B concentration measured up to 49 days after dosing of Am**B**isome, 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.

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.

Metabolism

The metabolic pathways of amphotericin B after administration of Am**B**isome are not known.

Excretion

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

Pharmacokinetics in Special Populations

Renal Impairment

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

Hepatic Impairment

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

Pediatric and Elderly Patients

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

Gender and Ethnicity

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

INDICATIONS AND USAGE

AmBisome is indicated for the following:

- 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 deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate.
- Treatment of visceral leishmaniasis. In immunocompromised patients with visceral leishmaniasis treated with AmBisome, relapse rates were high following initial clearance of parasites (see **DESCRIPTION OF CLINICAL STUDIES**).

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

DESCRIPTION OF CLINICAL STUDIES

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

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

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

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

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

Empirical Therapy in Febrile Neutropenic Patients

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

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

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%)

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

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

The incidence of mycologically confirmed and clinically diagnosed, emergent fungal infections are presented in the following table. AmBisome and amphotericin B were found to be equivalent with 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 on e dose of study drug	343	344
Mycologically confirmed fungal infection	11 (3.2%)	27 (7.8%)
Clinically diagnosed fungal infection	32 (9.3%)	16 (4.7%)
Total emergent Fungal infections	43 (12.5%)	43 (12.5%)

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

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

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

Treatment of Cryptococcal Meningitis in HIV Infected Patients.

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

years of age to complete 10 weeks of protocol-directed therapy. For mycologically 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	35/60 (58.3%) 97.5% CI[1]= -9.4%, +31%	36/75 (48%) 97.5% CI[1]= -18.8%, +19.8%	29/61 (47.5 %)

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

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

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.

Treatment of Visceral Leishmaniasis

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

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

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**

		Clearance at EOT	(%) at 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)

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

Laboratory Tests

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

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.

Other Nephrotoxic Medications

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

Skeletal Muscle Relaxants

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy Category B

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

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

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

The incidence of common adverse events (incidence of 10% or greater) occurring with AmBisome compared to amphotericin B deoxycholate, regardless of relationship to study drug, is 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	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

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

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

The following adverse events are based on the experience of 244 patients (202 adult and 42 pediatric patients) of whom 85 patients were treated with

AmBisome 3 mg/kg, 81 patients were treated with AmBisome 5 mg/kg and 78 patients treated with amphotericin B lipid complex 5 mg/kg in Study 97-0-034, a randomized double-blind, multi-center study in febrile, neutropenic patients. AmBisome and amphotericin B lipid complex were infused over two hours. The incidence of adverse events occurring in more than 10% of subjects in one or more arms regardless of relationship to study drug are summarized in the following table:

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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	7.1	8.6	12.8
increased	16.5	11.1	11.5
Bilirubinemia	20	18.5	28.2
BUN increased	20	18.5	48.7
Creatinine increased	12.9	12.3	12.8
Edema	8.2	8.6	14.1
Hyperglycemia	8.2	11.1	14.1
Hypervolemia	10.6	4.9	5.1
Hypocalcemia	37.6	43.2	39.7
Hypokalemia	15.3	25.9	15.4
Hypomagnesemia	10.6	7.4	11.5
Liver function tests abnormal			
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

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

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

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%)

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

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

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

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

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 (≥1.0°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%)

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°C	6 (7%)	8 (9%)	24 (28%)
Patients with chills/rigors	5 (6%)	8 (9%)	42 (48%)
Patients with nausea	11 (13%)	13 (14%)	18 (20%)
Patients with vomiting	14 (16%)	13 (14%)	16 (18%)
Respiratory adverse events	0	1 (1%)	8 (9%)

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

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

Toxicity and Discontinuation of Dosing

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

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

Less Common Adverse Events

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

Body as a Whole

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

Cardiovascular System

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

Digestive System

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

Hemic & Lymphatic System

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

Metabolic & Nutritional Disorders

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

Musculoskeletal System
Arthralgia, bone pain, dystonia, myalgia, and rigors.

Nervous System
Agitation, coma, convulsion, cough, depression, dysesthesia, dizziness, hallucinations, nervousness, paresthesia, somnolence, thinking abnormality, and tremor.

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

Skin & Appendages
Alopecia, dry skin, herpes simplex, injection site inflammation, maculopapular rash, purpura, skin discoloration, skin disorder, skin ulcer, urticaria, and vesiculobullous rash.

Special Senses
Conjunctivitis, dry eyes, and eye hemorrhage.

Urogenital System
Abnormal renal function, acute kidney failure, acute renal failure, dysuria, kidney failure, toxic nephropathy, urinary incontinence, and vaginal hemorrhage.

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

Clinical Laboratory Values
The effect of Am**B**isome 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 Am**B**isome 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.

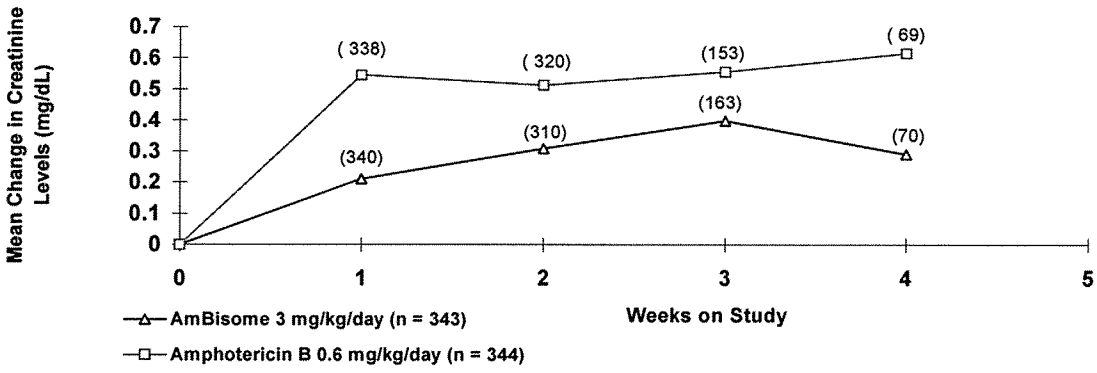
Incidence of nephrotoxicity, mean peak serum creatinine concentration, mean change from baseline in serum creatinine, and, incidence of hypokalemia in the double-blind randomized study were lower in the Am**B**isome group as summarized in the following table:

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%)

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:

Mean Change in Creatinine Over Time in Study 94-0-002

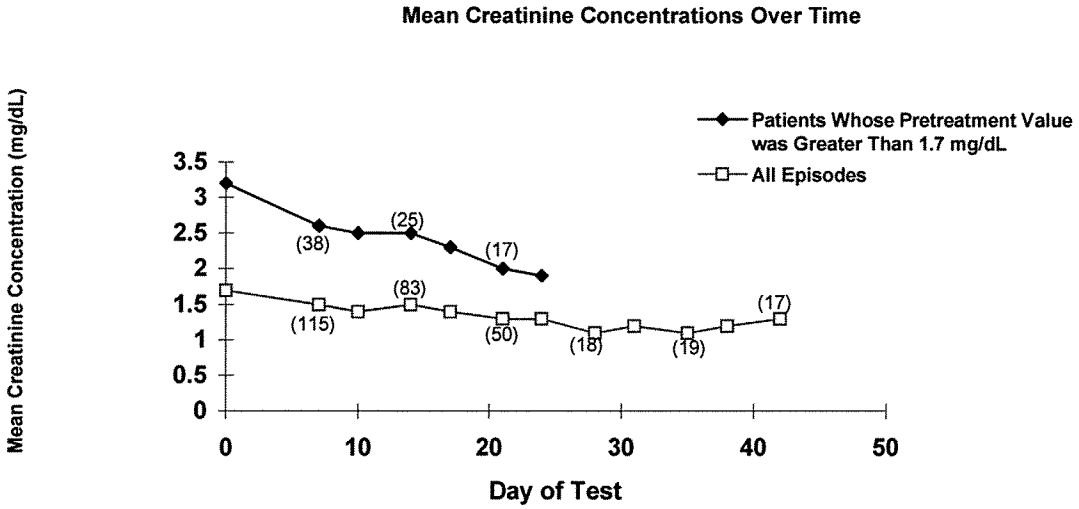


In empirical therapy study 97-0-034, the incidence of nephrotoxicity as measured by increases of serum creatinine from baseline was significantly lower for patients administered AmBisome (individual dose groups and combined) compared with amphotericin B lipid complex.

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%)

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.



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:

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%)

OVERDOSAGE

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

Management

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

Doses recommended for visceral leishmaniasis are presented below:

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

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

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

Directions for Reconstitution, Filtration and Dilution
Read This Entire Section Carefully Before Beginning Reconstitution
AmBisome **must** be reconstituted using Sterile Water for Injection, USP (without a bacteriostatic agent). Vials of AmBisome containing 50 mg of amphotericin B are prepared as follows:

Reconstitution
1. Aseptically add 12 mL of Sterile Water for Injection, USP to each AmBisome vial to yield a preparation containing 4 mg amphotericin B/mL.
   CAUTION: DO NOT RECONSTITUTE WITH SALINE OR ADD SALINE TO THE RECONSTITUTED CONCENTRATION, OR MIX WITH OTHER DRUGS. The use of any solution other than those recommended, or the presence of a bacteriostatic agent in the solution, may cause precipitation of AmBisome.

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

Filtration and Dilution

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

STORAGE OF AMBISOME

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

Storage of Reconstituted Product Concentrate

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

Storage of Diluted Product

Injection of Am**B**isome should commence within 6 hours of dilution with 5% Dextrose Injection.

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

HOW SUPPLIED

Am**B**isome for Injection is available as single cartons (equivalent to 50mg amphotericin B) and in packs of ten individual vial cartons (NDC 0469-3051-30).

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

Rx only

Marketed by:
Astellas Pharma US, Inc.
Deerfield, IL 60015-2548

Manufactured by:
Gilead Sciences, Inc.
San Dimas, CA 91773

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