PRODUCT MONOGRAPH

AMPHOTEC®

(Amphotericin B Cholesteryl Sulfate Complex for Injectable Suspension)

50 mg and 100 mg Amphotericin B per vial

THERAPEUTIC CLASSIFICATION

Antifungal Agent

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ACTION and CLINICAL PHARMACOLOGY

The active ingredient of AMPHOTEC®, amphotericin B, is a polyene antibiotic that acts by binding to sterols (primarily ergosterol) in cell membranes of sensitive fungi, with subsequent leakage of intracellular contents and cell death due to changes in membrane permeability. Amphotericin B also binds to the sterols (primarily cholesterol) in mammalian cell membranes, which is believed to account for its toxicity in animals and humans.

AMPHOTEC® (Amphotericin B Cholesteryl Sulfate Complex for Injectable Suspension) is a unique formulation and consists of a 1:1 (molar ratio) complex of amphotericin B and cholesteryl sulfate. Upon reconstitution, AMPHOTEC® forms a colloidal dispersion of microscopic disc-shaped particles.

Note: The liposomal encapsulation or incorporation into a lipid complex can substantially affect a drug's functional properties relative to those of non-encapsulated drug or non-lipid associated drug. Although the various liposomal and lipid-complexed products all contain amphotericin B, they differ significantly in their chemical composition, stability, and physical form of the lipid component and resultant pharmacokinetic profiles of amphotericin B.

Pharmacokinetics (see PHARMACOLOGY-Pharmacokinetics)

The pharmacokinetics of amphotericin B administered as AMPHOTEC® are best described by an open, two-compartment structural model with non-linear elimination. For AMPHOTEC®, the steady state volume of distribution (Vss) and total plasma clearance (CLt) increased with escalating doses, resulting in less than proportional increases in plasma concentration. Following a 1 mg/kg/hour infusion of AMPHOTEC®, 25 ± 18% (mean ± SD) of the total amphotericin B concentration in the plasma was in the AMPHOTEC® complex, dropping off to 9.3 ± 7.9% at 1 hour and 7.5 ± 9.3% after 24 hours. AMPHOTEC® pharmacokinetics were not related to baseline serum creatinine clearance, baseline liver function, or age of the patient. The increased volume of distribution probably reflected uptake by tissues.

Predicted Pharmacokinetic Parameters of Amphotericin B after Administration of Multiple Doses of AMPHOTEC® [a]

Mean Pharmacokinetic Parameter [b]	AMPHOTEC® (mg/kg/day)	
	3	4
Vss (L/kg)	3.8	4.1
CLt (L/h/kg)	0.105	0.112
Distribution Half-Life (minutes)	3.5	3.5
Elimination Half-Life (hours)	27.5	28.2
Cmax (µg/mL)	2.6	2.9
AUCss (µg/mL•h)	29	36

[a] Data obtained using population modeling in 51 bone marrow transplant patients. The modeling assumes amphotericin B pharmacokinetics after administration of AMPHOTEC® is best described by a 2-compartment model. Infusion rate = 1 mg/kg/hour.

[b] Vss = volume of distribution at steady-state.
CLt = total plasma clearance.
Cmax = maximum plasma concentration in the plasma achieved at the end of an infusion.
AUCss= area under the plasma concentration time curve at steady-state.

INDICATIONS AND CLINICAL USE

AMPHOTEC® is indicated for the treatment of invasive aspergillosis in cases where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses, and in cases where prior amphotericin B deoxycholate therapy has failed.

The indication of AMPHOTEC® as second-line therapy for the treatment of invasive aspergillosis is primarily based on a subset of patients from 5 open-label, noncomparative studies, one of which included emergency-use patients. The patients were treated with AMPHOTEC® because of failure to respond to amphotericin B deoxycholate (n = 49), development of nephrotoxicity while receiving amphotericin B deoxycholate (n = 62), preexisting renal impairment (n = 25), or other reasons (n = 25). A retrospective analysis was conducted in which "complete response" was defined as resolution of all attributable symptoms, signs, and radiographic abnormalities present at enrollment, and a

"partial response" was defined as major improvement of the above-mentioned parameters. The total number of responders was defined as the sum of the number of "complete" and "partial" responses. The response rate for evaluable patients was 46% (see Clinical Studies).

CONTRAINDICATIONS

AMPHOTEC® should not be administered to patients who have documented hypersensitivity to any of its components, unless, in the opinion of the physician, the advantages of using AMPHOTEC® outweigh the risks of hypersensitivity.

WARNINGS

Anaphylaxis has been reported with amphotericin B deoxycholate and other amphotericin B-containing drugs. Immediate treatment of anaphylaxis or anaphylactoid reactions is required. Epinephrine, oxygen, intravenous steroids, and airway management should be administered as indicated. If severe respiratory distress occurs, the infusion should be immediately discontinued. The patient should not receive further infusions of AMPHOTEC®.

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

PRECAUTIONS

General

As with any amphotericin B-containing product, during initial dosing of AMPHOTEC®, the drug should be administered intravenously under close clinical observation by medically trained personnel.

Acute infusion-related reactions including fever, chills, hypoxia, hypotension, nausea, or tachypnea may occur 1 to 3 hours after starting the intravenous infusion. These reactions are usually more severe or more frequent with the initial doses of AMPHOTEC® and usually diminish with subsequent doses. Acute infusion-related reactions can be managed by pretreatment with antihistamines and corticosteroids and/or by reducing the rate of infusion and by prompt administration of antihistamines and corticosteroids. (See **ADVERSE REACTIONS**).

Rapid intravenous infusion should be avoided.

Despite generally less nephrotoxicity of AMPHOTEC® at the recommended doses compared with amphotericin B deoxycholate at the dose range of 0.8 to 1.0 mg/kg/day, dose-limiting renal toxicity may still be observed with AMPHOTEC®.

Laboratory tests, particularly tests of renal and hepatic function, serum electrolytes, complete blood count and prothrombin time should be monitored as medically indicated.

Drug Interactions

No formal drug interaction studies have been conducted with AMPHOTEC®. When administered concomitantly, the following drugs are known to interact with amphotericin B; therefore the following drugs may interact with AMPHOTEC®.

Antineoplastic agents: Concurrent use of antineoplastic agents and amphotericin B may enhance the potential for renal toxicity, bronchospasm, and hypotension. Caution is urged when antineoplastic agents are given concomitantly with AMPHOTEC®.

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

Cyclosporine and Tacrolimus: In a randomized, double-blinded empiric trial to compare AMPHOTEC® and amphotericin B deoxycholate, patients with normal baseline serum creatinine levels were prospectively enrolled into four strata: adults receiving cyclosporine or tacrolimus (n = 89); or pediatric patients (< 16 years old) receiving cyclosporine or tacrolimus (n = 15); adults not receiving cyclosporine or tacrolimus (n =75); or pediatric patients not receiving cyclosporine or tacrolimus (n =34). Patients were assessed for renal toxicity defined as either a doubling or an increase of 1.0 mg/dL or more from baseline serum creatinine, or ≥ 50% decrease from baseline calculated creatinine clearance. Adults and pediatric patients receiving cyclosporine or tacrolimus in addition to AMPHOTEC® had a significantly lower rate of renal toxicity (31%, 16/51), compared to the amphotericin B deoxycholate patients receiving cyclosporine or tacrolimus (68%, 34/50). In the adults and pediatric patients not receiving cyclosporine or tacrolimus, only 8% (4/51) of the AMPHOTEC® patients experienced renal toxicity compared to 35% (17/49) of the amphotericin B deoxycholate patients.

Digitalis glycosides: Concurrent use of amphotericin B may induce hypokalemia and may potentiate digitalis toxicity. If digitalis glycosides are administered concomitantly with AMPHOTEC®, serum potassium levels should be closely monitored.

Flucytosine: Concurrent use of flucytosine with amphotericin B-containing preparations may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion. Caution is urged when flucytosine is given concomitantly with AMPHOTEC®.

Imidazoles (e.g., ketoconazole, miconazole, clotrimazole, fluconazole, etc.): Antagonism between amphotericin B and imidazole derivatives such as miconazole and ketoconazole which inhibit ergosterol synthesis, has been reported in both *in vitro* and *in vivo* animal studies. The clinical significance of these findings has not been determined.

Other nephrotoxic medications: Concurrent use of amphotericin B and agents such as aminoglycosides and pentamidine may enhance the potential for drug-induced renal toxicity. Caution is urged if aminoglycosides or pentamidine are used concomitantly with AMPHOTEC®. 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. If skeletal muscle relaxants are administered concomitantly with AMPHOTEC®, serum potassium levels should be closely monitored.

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long-term studies in animals have been performed with AMPHOTEC® or amphotericin B deoxycholate to evaluate carcinogenic potential. AMPHOTEC® and/or amphotericin B were not mutagenic *in vitro* with and without an exogenous mammalian microsomal metabolic activation system when assayed in the *Salmonella* reverse mutation assay, the CHO chromosomal aberration assay and the mouse lymphoma forward mutation assay. AMPHOTEC® was also negative *in vivo* in the mouse bone marrow micronucleus assay. No studies have been conducted to determine if AMPHOTEC® affects fertility or if it produces adverse effects when administered peri- or post-natally in animals. In multiple dose toxicity studies of up to 13 weeks in rats at doses up to 0.5 times the recommended human dose and in dogs at doses up to 0.4 times the recommended human dose (based on body surface area), ovarian and testicular histology were unaffected.

Pregnancy

Teratogenic Effects. There are no reports of pregnant women having been treated with AMPHOTEC®. Reproduction studies in rats at doses up to 0.4 times the recommended human dose and in rabbits at doses up to 1.1 times the recommended human dose have revealed no evidence of harm to the fetus due to treatment with AMPHOTEC®. Because animal reproduction studies are not always predictive of human response and because adequate and well controlled studies have not

been conducted in pregnant women, AMPHOTEC® should be used during pregnancy only if the anticipated benefit to the patient outweighs the potential risk to the fetus.

Nursing Mothers

It is not known whether AMPHOTEC® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from amphotericin B, a decision should be made to discontinue nursing or discontinue treatment with AMPHOTEC®, taking into account the importance of the drug to the mother.

Pediatric Use

Ninety-seven pediatric patients with systemic fungal infections have been treated with AMPHOTEC®, at daily doses (mg/kg) similar to those given to adults. No unexpected adverse events have been reported.

Geriatric Use

Sixty-eight patients of at least 65 years of age have been treated with AMPHOTEC®. No unexpected adverse events have been reported.

Patients with Special Diseases or Conditions

Hepatic Impairment: The effect of hepatic impairment on the disposition of AMPHOTEC® is not known. The metabolic pathways of AMPHOTEC® are not known (see also PHARMACOLOGY - Pharmacokinetics in Humans).

Renal Impairment: The effect of renal impairment on the disposition of AMPHOTEC® is not known (see also PHARMACOLOGY - Pharmacokinetics in Humans).

ADVERSE REACTIONS

The following adverse events are based on the experience of 572 AMPHOTEC®-treated patients from 5 open studies of patients with systemic fungal infections, of whom 526 were treated with a

daily dose of 3 - 6 mg/kg. Additionally, comparative adverse event data from 150 AMPHOTEC® (4 or 6 mg/kg/day) and 146 amphotericin B deoxycholate (0.8 or 1 mg/kg/day) patients in prospectively randomized double-blinded studies of empiric treatment of febrile and neutropenic patients or treatment of aspergillosis are also provided.

Infusion-related adverse events: Infusion-related adverse events occurred most frequently in association with the first infusion of AMPHOTEC® (see PRECAUTIONS, General). Their frequency and severity decreased with subsequent dosing. Based on the combined non-comparative studies, 35% (197/569) of the patients reported chills or chills and fever, possibly or probably related to AMPHOTEC®, on the first day of dosing, compared to 14% (58/422) by the seventh dose. In the comparative studies, a similar decreasing trend was noted for AMPHOTEC® and amphotericin B deoxycholate.

Summary of Probably and Possibly Related Adverse Events Reported by ≥5% of AMPHOTEC® Patients (% of Patients Experiencing the Adverse Event)

Adverse Event	Non-Comparative Studies		Comparative Studies [a]	
	AMPHOTEC® (n = 572)	AMPHOTEC® Aspergillosis Patients (n = 161)	AMPHOTEC® (n = 150)	Amphotericin B Deoxycholate (n = 146)
Dose (mg/kg/day)	mainly 3-6		4 or 6	0.8 or 1.0
Body as a Whole				
Chills	50	55	77	56
Fever	33	34	55	47
Headache	5	8	4	3
Chills and fever	3	3	7	2
Cardiovascular System				
Hypotension	10	9	12	5
Tachycardia	10	12	9	5
Hypertension	7	9	7	6
Digestive System				
Nausea	8	12	7	7

Adverse Event	AMPHOTEC® (n = 572)	AMPHOTEC® Aspergillosis Patients (n = 161)	AMPHOTEC® (n = 150)	Amphotericin B Deoxycholate (n = 146)
Nausea and vomiting	7	11	4	7
Vomiting	6	8	11	8
Liver function test abnormal	4	4	11	8
Hemic and Lymphatic System				
Thrombocytopenia	6	7	1	1
Metabolic/Nutritional Disorders				
Creatinine increased [b]	12	12	21	34
Hypokalemia	8	7	26	29
Hypomagnesemia	4	7	6	11
Hyperbilirubinemia	3	2	19	17
Alkaline phosphatase increased	3	3	7	8
Hyperglycemia	1	1	6	9
Respiratory System				
Dyspnea	5	4	9	4
Hypoxia	5	6	9	5

[a] From AMPHOTEC (4 or 6 mg/kg/day) and amphotericin B deoxycholate (0.8 or 1 mg/kg/day) patients in prospectively randomized double-blinded studies of empiric treatment of febrile and neutropenic patients or treatment of first-line aspergillosis, respectively.

[b] Includes patients with “kidney function abnormal” which was associated with an increase in creatinine.

The following adverse events also occurred in AMPHOTEC® patients; however, the causal relationship of these adverse events is uncertain:

	≥ 5% of Patients	1% to 5% of Patients
General (body as a whole)	abdomen enlarged, abdominal pain, back pain, chest pain, face edema, injection site inflammation, mucous membrane disorder, pain, sepsis	accidental injury, allergic reaction, asthenia, death, hypothermia, immune system disorder, infection, injection site pain, injection site reaction, neck pain
Cardiovascular system	cardiovascular disorder, hemorrhage, postural hypotension	arrhythmia, atrial fibrillation, bradycardia, congestive heart failure, heart arrest, phlebitis, shock, supraventricular tachycardia, syncope, vasodilatation, venoocclusive liver disease, ventricular extrasystoles
Digestive system	diarrhea, dry mouth, hematemesis, jaundice, stomatitis	anorexia, bloody diarrhea, constipation, dyspepsia, fecal incontinence, gamma glutamyl transpeptidase increased, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, glossitis, hepatic failure, melena, mouth ulceration, oral moniliasis, rectal disorder
Hemic and lymphatic system	anemia, coagulation disorder, prothrombin decreased	ecchymosis, fibrinogen increased, hypochromic anemia, leukocytosis, leukopenia, petechia, thromboplastin decreased
Metabolic and nutritional disorders	edema, generalized edema, hypocalcemia, hypophosphatemia, peripheral edema, weight gain	acidosis, BUN increased, dehydration, hyponatremia, hyperkalemia, hyperlipemia, hypernatremia, hypervolemia, hypoglycemia, hypoproteinemia, lactic dehydrogenase increased, SGOT increased, SGPT increased, weight loss
Musculoskeletal system		arthralgia, myalgia
Nervous system	confusion, dizziness, insomnia, somnolence, thinking abnormal, tremor	agitation, anxiety, convulsion, depression, hallucinations, hypertonia, nervousness, neuropathy, paresthesia, psychosis, speech disorder, stupor
Respiratory system	apnea, asthma, cough increased, epistaxis, hyperventilation, lung disorder, rhinitis	hemoptysis, lung edema, pharyngitis, pleural effusion, respiratory disorder, sinusitis
Skin and appendages	maculopapular rash, pruritis, rash, sweating	acne, alopecia, petechial rash, skin discoloration, skin disorder, skin

	≥ 5% of Patients	1% to 5% of Patients
		nodule, skin ulcer, urticaria, vesiculobullous rash
Special senses	eye hemorrhage	amblyopia, deafness, ear disorder, tinnitus
Urogenital system	hematuria	albuminuria, dysuria, glycosuria, kidney failure, oliguria, urinary incontinence, urinary retention, urinary tract disorder

SYMPTOMS AND TREATMENT OF OVERDOSAGE

AMPHOTEC® is not dialyzable. Amphotericin B deoxycholate overdose has been reported to result in cardio-respiratory arrest.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and children is 3-4 mg/kg as required, once a day.

AMPHOTEC®, reconstituted in Sterile Water for Injection, is administered diluted in 5% Dextrose Injection by intravenous infusion at a rate of 1 mg/kg/hour. A test dose immediately preceding the first dose is advisable when commencing all new courses of treatment. A small amount of drug (e.g., 10 mL of the final preparation containing between 1.6 to 8.3 mg) should be infused over 15 to 30 minutes and the patient carefully observed for the next 30 minutes.

The infusion time may be shortened to a minimum of 2 hours for patients who show no evidence of intolerance or infusion-related reactions. If the patient experiences acute reactions or cannot tolerate the infusion volume, the infusion time may be extended.

Renal Impairment: Renal toxicity of AMPHOTEC®, as measured by serum creatinine levels has been shown to be dose dependent. There are no firm guidelines for dose adjustment based on laboratory tests and results and decisions about dose adjustment should be made only after taking

into account the overall clinical condition of the patient (see also PHARMACOLOGY-Pharmacokinetics [in Humans]).

Hepatic Impairment: No dose adjustment is required for patients with hepatic impairment (see also PHARMACOLOGY - Pharmacokinetics in Humans).

Directions for Reconstitution and Preparation of Infusion Admixture

AMPHOTEC® must be reconstituted by addition of Sterile Water for Injection. Using sterile syringe and a 20-gauge needle, rapidly add the following volumes to the vial to provide a liquid containing 5 mg of amphotericin B per mL. Shake gently by hand, rotating the vial until all solids have dissolved. Note that the suspension should be a translucent yellow suspension free of particulates and precipitates.

50 mg/vial add 10 mL Sterile Water for Injection
100 mg/vial add 20 mL Sterile Water for Injection

For infusion, further dilute the reconstituted liquid to a final concentration of approximately 0.6 mg/mL (range 0.16 mg/mL to 0.83 mg/mL). The following table provides dilution recommendations:

Dose of AMPHOTEC®	Volume of Reconstituted AMPHOTEC®	Infusion Bag Size for 5% Dextrose Injection
10 - 35 mg	2 - 7 mL	50 mL
35 - 70 mg	7 - 14 mL	100 mL
70 - 175 mg	14 - 35 mL	250 mL
175 - 350 mg	35 - 70 mL	500 mL
350 - 1000 mg	70 - 200 mL	1000 mL

Do not reconstitute the lyophilized powder with saline or dextrose solutions, or admix the reconstituted liquid with saline or electrolytes. The use of any solution other than those

recommended, or the presence of a bacteriostatic agent (e.g., benzyl alcohol) in the solution may cause precipitation of AMPHOTEC®. **Do not filter or use an in-line filter with AMPHOTEC®.**

Do not mix the infusion admixture with other drugs. If administered through an existing intravenous line, flush with 5% Dextrose Injection prior to, and following, infusion of AMPHOTEC®, otherwise administer via a separate line.

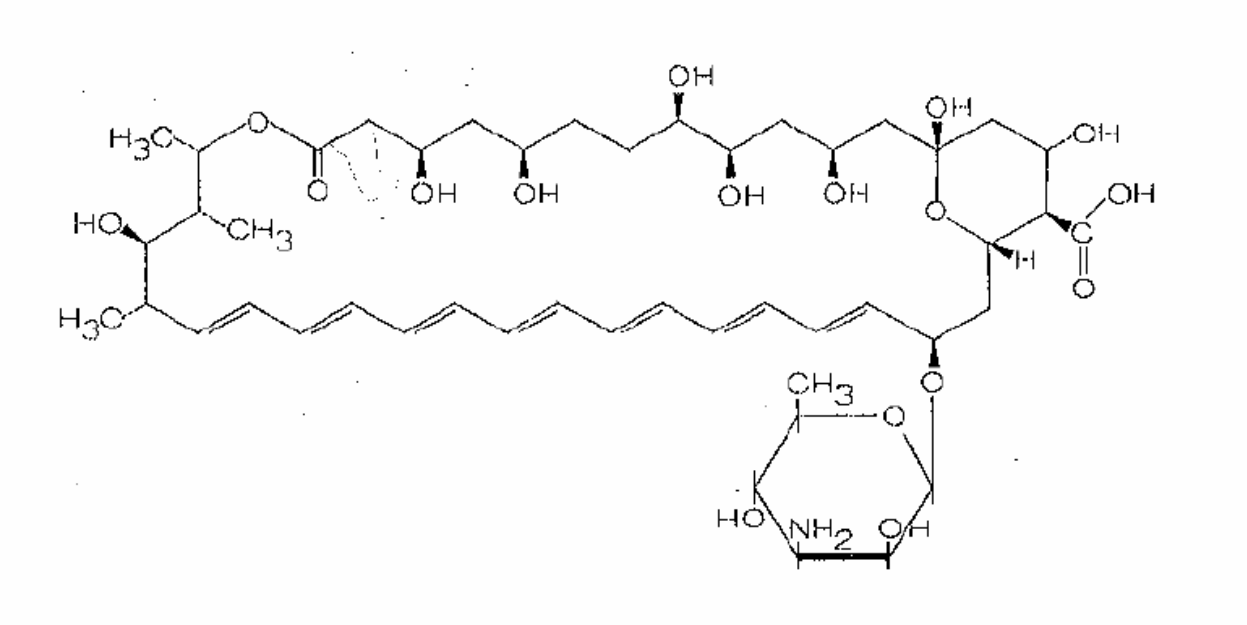
PHARMACEUTICAL INFORMATION

Drug Substance

Amphotericin B has a molecular formula of $C_{47}H_{73}NO_{17}$; its molecular weight is 924.10.

The approved chemical name is:
[1R-(1*R**, 3*S**, 5*R**, 6*R**, 9*R**, 11*R**, 15*S**, 16*R**, 17*R**, 18*S**, 19*E*, 21*E*, 23*E*, 25*E*, 27*E*, 29*E*, 31*E*, 33*R**, 35*S**, 36*R**, 37*S**)]-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.

Amphotericin B has the following structure:



Description

Amphotericin B is a bright yellow free-flowing crystalline powder. It is moderately soluble in water and methanol, becoming more soluble with acidic or basic pH. Amphotericin B decomposes gradually above 170°C. The pKa is about 5.7 (carboxylic acid at internal hemiketal ring) and about 10 (primary amino group on mycosamine moeity).

Composition

AMPHOTEC® consists of a 1:1 (molar ratio) complex of amphotericin B and cholesteryl sulfate. Upon reconstitution, AMPHOTEC® forms a colloidal dispersion of microscopic disc-shaped particles. Amphotericin B is an antifungal polyene antibiotic produced by a strain of *Streptomyces nodosus*.

AMPHOTEC® is available in 50 mg and 100 mg single dose vials, as a sterile, nonpyrogenic, lyophilized powder.

Each vial contains:

	50 mg vial	100 mg vial
Amphotericin B	50 mg	100 mg
Sodium cholesteryl sulfate	26.4 mg	52.8 mg
Tromethamine	5.64 mg	11.28 mg
Disodium edetate dihydrate	0.372 mg	0.744 mg
Lactose monohydrate	950 mg	1900 mg
Hydrochloric acid (buffer)	q.s.	q.s.

Stability and Storage Recommendations

Store unopened vials of AMPHOTEC® at 15-30°C. AMPHOTEC® should be retained in the carton until time of use. After reconstitution, the drug should be refrigerated at 2-8°C and used within 24 hours. **Do not freeze.** After further dilution with 5% Dextrose Injection, the infusion should be stored in a refrigerator (2-8°C) and used within 24 hours. Partially used vials should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if a precipitate or foreign matter is present, or if the seal is not intact. Strict aseptic technique should always be observed during reconstitution and dilution since no preservatives are present in the lyophilized drug or in the solutions used for reconstitution and dilution.

AVAILABILITY OF DOSAGE FORMS

AMPHOTEC® (Amphotericin B Cholesteryl Sulfate Complex for Injectable Suspension) is a sterile lyophilized powder supplied in single use glass vials. Each vial is individually packaged.

AMPHOTEC®	50 mg	(in 20 mL vial)	(DIN 02241750)
AMPHOTEC®	100 mg	(in 50 mL vial)	(DIN 02241749)

MICROBIOLOGY

Activity *in vitro* and *in vivo*

AMPHOTEC® is active *in vitro* against *Aspergillus* and *Candida* species. One hundred and twelve clinical isolates of four different *Aspergillus* species and 88 clinical isolates of five different *Candida* species were tested, with a majority of minimum inhibitory concentrations (MICs) < 1 µg/mL. AMPHOTEC® is also active *in vitro* against other fungi. *In vitro* AMPHOTEC® is fungistatic or fungicidal, depending upon the concentration of the drug and the susceptibility of the fungal organism. However, standardized techniques for susceptibility testing for antifungal agents have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

AMPHOTEC® is active in murine models against *Aspergillus fumigatus, Candida albicans*, *Coccidioides immitis* and *Cryptococcus neoformans*, and in an immunosuppressed rabbit model of aspergillosis, in which the endpoints were prolonged survival of infected animals and clearance of microorganisms from target organ(s). AMPHOTEC® also was active in a hamster model of visceral leishmaniasis, a disease caused by infection of macrophages of the mononuclear phagocytic system by a protozoal parasite of the genus *Leishmania*. In this hamster model the endpoints were also prolonged survival of infected animals and clearance of microorganisms from target organ(s).

Drug Resistance

Variants with reduced susceptibility to amphotericin B have been isolated from several fungal species after serial passage in cell culture media containing the drug and from some patients receiving prolonged therapy with amphotericin B deoxycholate. Although the relevance of drug resistance to clinical outcome has not been established, fungal organisms that are resistant to amphotericin B may also be resistant to AMPHOTEC®.

PHARMACOLOGY

Pharmacokinetics in Humans

The pharmacokinetics of amphotericin B, administered as AMPHOTEC®, were studied in 51 bone marrow transplant patients with systemic fungal infections. The median (range) age and weight of those patients were 32 (3 to 52) years and 69.5 (14 to 116) kg, respectively. AMPHOTEC® doses ranged from 0.5 to 8.0 mg/kg/day. The assay used in this study to measure amphotericin B in plasma does not distinguish amphotericin B that is complexed with cholesteryl sulfate from uncomplexed amphotericin B.

A population modeling approach was used to estimate pharmacokinetic parameters (see table). The pharmacokinetics of amphotericin B, administered as AMPHOTEC®, were best described by an open, two-compartment structural model with nonlinear elimination. Steady state volume of distribution (Vss) and total plasma clearance (CLt) increased with escalating doses, resulting in less than proportional increases in plasma concentration over a dose range of 0.5 to 8.0 mg/kg/day. The increased volume of distribution probably reflected uptake by tissues. The covariates of body weight and dose level accounted for a substantial portion of the variability of the pharmacokinetic estimates between patients. The unexplained variability in clearance was 26%. Based on the population model developed for these patients, pharmacokinetic parameters were predicted for two doses of AMPHOTEC® and are provided in the following table:

Predicted Pharmacokinetic Parameters of Amphotericin B after Administration of Multiple Doses of AMPHOTEC® [a]

Mean Pharmacokinetic Parameter [b]	AMPHOTEC® (mg/kg/day)	
	3	4
Vss (L/kg)	3.8	4.1
CLt (L/h/kg)	0.105	0.112
Distribution Half-Life (minutes)	3.5	3.5
Elimination Half-Life (hours)	27.5	28.2
Cmax (µg/mL)	2.6	2.9
AUCss (µg/mL•h)	29	36

[a] Data obtained using population modeling in 51 bone marrow transplant patients. The modeling assumes amphotericin B pharmacokinetics administration of AMPHOTEC® is best described by a 2-compartment model. Infusion rate = 1 mg/kg/hour.

[b] Vss = volume of distribution at steady-state.
CLt = total plasma clearance.
Cmax = maximum plasma concentration in the plasma achieved at the end of an infusion.
AUCss= area under the plasma concentration time curve at steady-state.

In addition, the pharmacokinetics of amphotericin B, administered as amphotericin B deoxycholate, were studied in 15 patients in whom amphotericin B was administered for the treatment of aspergillus infections or empiric therapy. The median (range) age and weight for these patients were 21 (4 to 66) years and 60 (19 to 117) kg, respectively. The pharmacokinetics of amphotericin B, administered as amphotericin B deoxycholate, was best described as an open, two-compartment model with linear elimination. The predicted pharmacokinetic parameters are provided in the following table:

Predicted Pharmacokinetic Parameters of Amphotericin B after Administration of Multiple Doses of 1 mg/kg Amphotericin B Deoxycholate [a]

Mean Pharmacokinetic Parameter [b]	Amphotericin B Deoxycholate
Vss (L/kg)	1.1
CLt (L/h/kg)	0.028
Distribution Half-Life (minutes)	38
Elimination Half-Life (hours)	39
Cmax (µg/mL)	2.9
AUCss (µg/mL•h)	36

[a] Data obtained using population modeling in 15 patients in whom amphotericin B deoxycholate was administered for treatment of aspergillus infection or empiric therapy. The modeling assumes amphotericin B pharmacokinetics after administration of amphotericin B deoxycholate are best described by a 2-compartment model. Infusion rate = 0.25 mg/kg/hour.

[b] Vss = volume of distribution at steady-state.
CLt = total plasma clearance.
Cmax = maximum plasma concentration in the plasma achieved at the end of an infusion.
AUCss= area under the plasma concentration time curve at steady-state.

An analytical assay that is able to distinguish between amphotericin B in the AMPHOTEC® complex and amphotericin B which is not complexed to cholesteryl sulfate was used to analyze samples from a study of 25 patients who were either immunocompromised with aspergillosis or both febrile and neutropenic. Following a 1 mg/kg/hour infusion 25 ± 18% (mean ± SD) of the total amphotericin B concentration measured in plasma was in the AMPHOTEC® complex, dropping to 9.3 ± 7.9% at 1 hour and 7.5 ± 9.3% at 24 hours after the end of the infusion.

Pharmacokinetics in Special Populations

A population modeling approach was used to assess the effect of renal function, hepatic function, and age on the pharmacokinetics of AMPHOTEC® in 51 patients receiving bone marrow transplants as described earlier.

Renal Impairment: The pharmacokinetics of amphotericin B, administered as AMPHOTEC®, were not related to baseline serum creatinine clearance in the population studied; the median (range) creatinine clearance for this population was 74.0 (range: 35 - 202) mL/min/70 kg. The effect of more severe renal impairment on the pharmacokinetics of AMPHOTEC® has not been studied.

Hepatic Impairment: The pharmacokinetics of amphotericin B, administered as AMPHOTEC®, were not related to baseline liver function, as determined by liver enzymes and total bilirubin. For the population tested, the mean ± SD values for AST and total bilirubin were 59.4 ± 70.0 IU/mL and 3.5 ± 3.7 mg/dL, respectively. The effect of more severe hepatic impairment on the pharmacokinetics of AMPHOTEC® has not been studied.

Age: The pharmacokinetics of amphotericin B, administered as AMPHOTEC®, were not related to the age of the patient. The median (range) age for the population in this study was 32 (3 to 52) years.

Clinical Studies

Data from 161 patients with proven or probable aspergillus infection were pooled from 5 non-comparative open label studies, one of which included emergency-use patients. The patients were treated with AMPHOTEC® because of failure to respond to amphotericin B deoxycholate (n = 49), development of nephrotoxicity while receiving amphotericin B deoxycholate (n = 62), preexisting renal impairment (n = 25), or other reasons (n = 25).

The median age of these 161 patients (92 males and 69 females) was 41 years (range 2 months - 85 years). For the 155 patients with baseline neutrophil data, 33 patients (21%) had neutrophil counts of < 500 /mm^3. The underlying diseases included bone marrow transplant, 69 (43%); hematological malignancy, 51(32%); solid organ transplant, 25 (15%); solid tumor, 3 (2%); and other diagnoses, 13 (8%) including surgery, 4; HIV infection, 3; immunosuppression for autoimmune disease, 3; diabetes, 2; and no known underlying disease, 1. Pulmonary involvement was the primary infection site, 118 patients (73%), followed by sinus, 14 (9%), CNS, 9 (6%), skin/wound, 9 (6%), and others,

10 (6%) including 3 with bone involvement, 2 with hepatic involvement, 2 with disseminated disease and 1 each with endocarditis, ophthalmitis, otitis, and involvement of the hard palate. The 49 patients enrolled due to failure to respond to amphotericin B had received amphotericin B deoxycholate prior to AMPHOTEC® for ≤7 days (11 patients), 8 - 14 days (16 patients), and > 14 days (22 patients).

Patients were defined by their physicians as being refractory to amphotericin B deoxycholate therapy based on overall clinical judgment after receiving either a minimum of 7 days of amphotericin B or a minimum total dose of 15 mg/kg of amphotericin B. Nephrotoxicity was defined as a serum creatinine that had doubled from baseline, increased by ≥1.5 mg/dL or increased to ≥ 2.0 mg/dL. Preexisting renal impairment was defined as a serum creatinine that had increased to ≥ 2.0 mg/dL due to reasons other than amphotericin B administration.

Classifications of diagnosis and response were based on the definitions previously developed by the Mycoses Study Group. A retrospective response analysis was conducted in which a "complete response" was defined as resolution of all attributable symptoms, signs, and radiographic abnormalities present at enrollment, and a "partial response" was defined as major improvement of the above-mentioned parameters. The total number of responders was the sum of the number of "complete" and "partial" responses.

Of the 161 patients, 80 were considered evaluable for response. Eighty-one (81) were excluded on the basis of inadequate diagnosis, confounding factors, or receiving ≤ 4 doses of AMPHOTEC®. In the evaluable patients the median daily dose was 4 mg/kg/day (range 0.73 - 7.5 mg/kg/day) and the cumulative median dose was 6.3 g (range 0.36 - 34.4 grams). Median duration of treatment was 24 days (range 5 - 129 days).

Response Rates for Evaluable Patients

Patient Group (n)	Complete Response	Partial Response	Total Responders [a]	Response Rate
Amphotericin B failure (28) [b]	3	9	12	43%
Nephrotoxicity (36) [c]	5	12	17	47%
Preexisting renal impairment (16) [d]	1	7	8	50%
Total (80)	9	28	37	46%

[a] Total responders = Complete responses + Partial responses.
[b] Defined, based on overall clinical judgment, after receiving a minimum of 7 days of amphotericin B or a minimum of total dose of 15 mg/kg of amphotericin B.
[c] Defined as a serum creatinine that had doubled from baseline or increased by ≥1.5 mg/dL or increased to ≥ 2.0 mg/dL.
[d] Defined as a serum creatinine that had increased to ≥ 2.0 mg/dL due to reasons other than amphotericin B.

There is no directly comparable control group for the patients described in the above table to be certain whether similar patients would have responded had amphotericin B deoxycholate therapy been continued. A randomized study comparing AMPHOTEC® with amphotericin B deoxycholate for therapy of invasive aspergillosis is currently undergoing analysis.

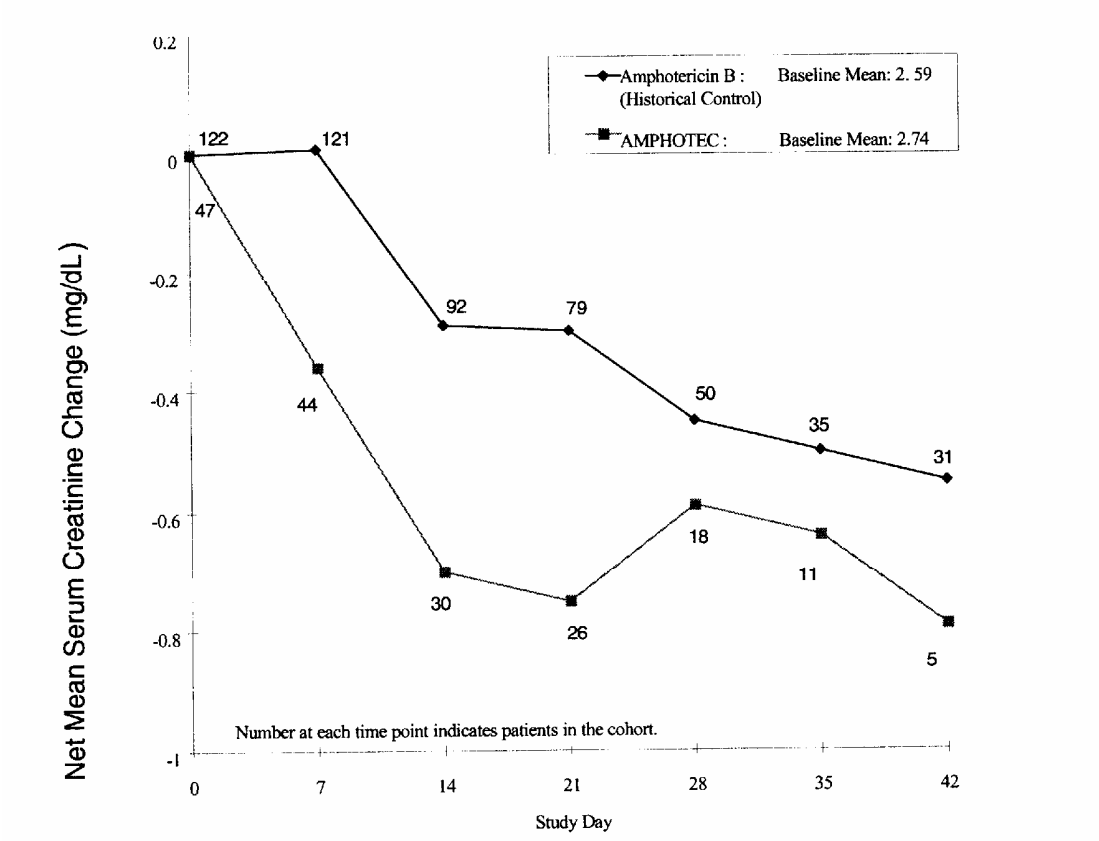
Renal Function

Patients with renal dysfunction at baseline:

The subset of patients with aspergillosis from the above five non-comparative open label studies, in whom AMPHOTEC® treatment was initiated when their serum creatinine was ≥ 2.0 mg/dL (n = 47) experienced a mean decline in serum creatinine during treatment. In part, this decline may be attributed to patient dropout over time from this group. A historical control group was selected by reviewing medical charts of patients from January 1990 to June 1994 at 6 medical centers (M.D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, H. Lee Moffitt Cancer Center, University of Pittsburgh, Memorial Sloan-Kettering Cancer Center, and Bone Marrow Transplant

Program at Emory University). The mean change in serum creatinine was evaluated for similar cohorts of patients from this historical control group, with the baseline for assessing change being the day each patient's serum creatinine reached ≥ 2.0 mg/dL. As shown in the figure, serum creatinine levels were lower during treatment with AMPHOTEC® when compared to the serum creatinine levels of amphotericin B deoxycholate patients in the historical control group. There is no directly comparable group to be certain whether this decline is significantly better than the results of serum creatinine levels in patients who had continued on amphotericin B deoxycholate. Since these data were obtained from two separate studies, no statistical testing of the differences between these two groups was performed.

Changes in Mean Serum Creatinine Over Time in Patients with Aspergillosis and Baseline Serum Creatinine ≥ 2.0 mg/dL [a,b]



[a] These curves do not represent the clinical course of a given patient, but that of an open-label cohort of patients.
[b] Amphotericin B refers to amphotericin B deoxycholate.

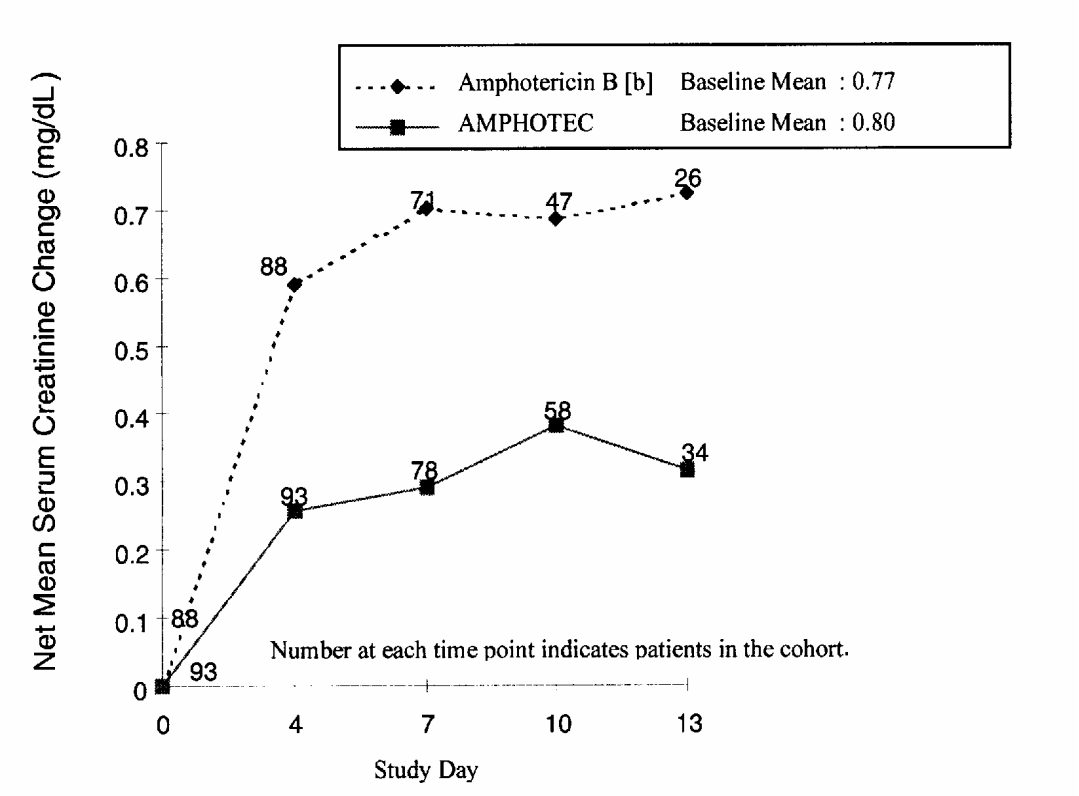
Patients with normal renal function at baseline:

In a randomized, double-blind, multicenter trial, neutropenic patients (n = 213) were treated empirically with either 4.0 mg/kg/day AMPHOTEC®, or 0.8 mg/kg/day amphotericin B deoxycholate intravenously, for up to 14 days. This study was designed to compare the safety profiles of the two treatments. **NOTE: AMPHOTEC® is NOT approved for empirical treatment in febrile neutropenic patients**.

Patients were assessed for renal toxicity defined as either a doubling or an increase of 1.0 mg/dL or more from baseline serum creatinine, or ≥ 50% decrease from baseline calculated creatinine clearance.

In this population, with largely normal renal function at baseline, median serum creatinine levels were 0.8 mg/dL for both treatment groups. The mean change in serum creatinine was evaluated for patients with baseline creatinine ≤ 1.5 mg/dL. As shown in the graph, patients in both treatment groups showed an increase in serum creatinine while on study, however AMPHOTEC® patients experienced significantly less creatinine increase.

Changes in Mean Serum Creatinine Over Time in Patients with Febrile Neutropenia, and Baseline Serum Creatinine ≤ 1.5 mg/dL [a]



[a] These curves do not represent the clinical course of a given patient, but that of a cohort of patients.
[b] Administered as amphotericin B deoxycholate.

Hypokalemia

In the same empiric study, significantly more amphotericin B deoxycholate patients had at least one laboratory result of serum potassium < 3.0 mEq/L at least one time in the study compared with AMPHOTEC® patients (23% vs. 7%). Concomitant supplemental potassium was allowed in the study design; both groups received approximately equal amounts of potassium supplementation.

Hypomagnesemia

In this study overall, there was no trend for decreasing serum magnesium in either treatment group.

TOXICOLOGY

Acute Toxicity

The acute intravenous toxicity of AMPHOTEC® in mice is at least 10 fold less lethal than amphotericin B deoxycholate.

LD_{50} in Male and Female Mice (mg/kg and 95% C.I.)

Formulation	Males	Females
AMPHOTEC®	36 (29-45)	38 (31-47)
Amphotericin B deoxycholate	2.6 (1.6- 4.4)	2.0 (1.4-2.9)

Multiple Dose Toxicity

Intravenous administration of 5.0 mg/kg/day AMPHOTEC® to rats for 28 days induced adverse effects, including hyperplasia of the epithelium of the renal pelvis and bladder mucosa, of similar severity and frequency to those observed after exposure to 1.0 mg/kg/day amphotericin B deoxycholate. AMPHOTEC® (1.0 mg/kg/day) induced similar adverse effects, but of lesser

incidence and severity compared to those induced by an equivalent dose of amphotericin B deoxycholate.

Intravenous administration of 2.5 to 7.5 mg/kg/day AMPHOTEC® to rats for 13 weeks induced a variety of mild to moderate clinical and histopathological changes consistent with mild renal and hepatic toxicity, and were similar to those seen with amphotericin B deoxycholate. Most of the changes were partially or completely reversible during a 45-day recovery period. A no-effect level was not established; however, changes in the 2.5 mg/kg AMPHOTEC® group were minimal to mild in severity and generally reversible.

Daily I.V. administration of up to 2.0 mg/kg AMPHOTEC®, or 0.4 mg/kg amphotericin B deoxycholate to male and female beagle dogs for 13 weeks resulted in, dose-related, reversible, mild renal toxicity. Amphotericin B deoxycholate–induced adverse effects of greater severity than AMPHOTEC®. There were no toxic effects unique to AMPHOTEC® observed in any of the studies.

Mutagenicity

AMPHOTEC® was tested for mutagenic potential in the *Salmonella* Reverse Mutation Assay (Ames Test) in the presence and absence of a mammalian microsomal metabolic activation system. No cytotoxicity was observed at doses up to 5000 mg/plate in either cytotoxicity assay. *In vivo*, AMPHOTEC® did not induce a significant increase in micronuclei in bone marrow polychromatic erythrocytes in the mouse micronucleus assay.

Carcinogenicity

No long-term studies in animals have been performed with AMPHOTEC® or amphotericin B deoxycholate to evaluate carcinogenic potential.

Embryotoxicity and Fertility

The potential developmental toxicity of AMPHOTEC® was evaluated in Sprague-Dawley rats and in New Zealand rabbits. The maternal no-observable-effect-level (NOEL) in pregnant rats was 2.5 mg/kg/day. Maternal toxicity, as reflected in reduced body weight gain and feed consumption, was

observed in the 5.0 and 7.5 mg/kg/day AMPHOTEC® dose groups. No adverse effects on embryo-fetal viability, growth or morphology were detected, and the developmental NOEL was greater than 7.5 mg/kg/day. The observed maternal NOEL of AMPHOTEC® in pregnant rabbits was less than 2.5 mg/kg/day. Maternal toxicity, as reflected by reduced body weight gain and feed consumption, was seen in all AMPHOTEC® treatment groups. No adverse effects on embryo-fetal viability, growth, or morphology were detected. The developmental NOEL was greater than 10.0 mg/kg/day.

Local Tolerance

The intravenous and intraarterial irritative potential of AMPHOTEC® was compared with amphotericin B deoxycholate in rabbits. AMPHOTEC® was better tolerated than amphotericin B deoxycholate, and with AMPHOTEC® the effects were reversible within 72 hours, whereas there was little resolution of the effects with amphotericin B deoxycholate.

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