

ABELCET®
(Amphotericin B Lipid Complex Injection)

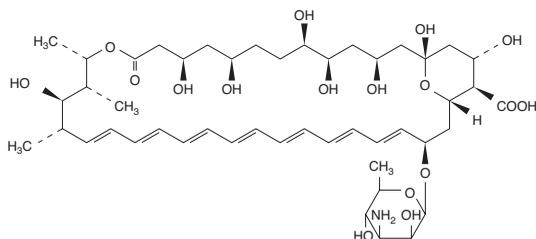
DESCRIPTION

ABELCET® is a sterile, pyrogen-free suspension for intravenous infusion. ABELCET® consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid molar ratio. The two phospholipids, L- α -dimyristoylphosphatidylcholine (DMPC) and L- α -dimyristoylphosphatidylglycerol (DMPG), are present in a 7:3 molar ratio. ABELCET® is yellow and opaque in appearance, with a pH of 5 - 7.

NOTE: Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed 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 functional properties of these drug products.

Amphotericin B is a 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.

It has a molecular weight of 924.09 and a molecular formula of C₄₇H₇₃NO₁₇. The structural formula is:



ABELCET® is provided as a sterile, opaque suspension in 20 mL glass, single-use vials. Each 20 mL vial contains 100 mg of amphotericin B (see DOSAGE AND ADMINISTRATION), and each mL of ABELCET® contains:

Amphotericin B USP	5 mg
L- α -dimyristoylphosphatidylcholine (DMPC)	3.4 mg
L- α -dimyristoylphosphatidylglycerol (DMPG)	1.5 mg
Sodium Chloride USP	9 mg
Water for Injection USP, q.s. 1 mL	

MICROBIOLOGY

Mechanism of Action

The active component of ABELCET®, amphotericin B, acts by binding to sterols in the cell membrane of susceptible fungi, with a resultant change in the permeability of the membrane. Mammalian cell membranes also contain sterols, and damage to human cells is believed to occur through the same mechanism of action.

Activity in vitro and in vivo

ABELCET® shows *in vitro* activity against *Aspergillus* sp. (n=3) and *Candida* sp. (n=10), with MICs generally <1 μ g/mL. Depending upon the species and strain of *Aspergillus* and *Candida* tested, significant *in vitro* differences in susceptibility to amphotericin B have been reported (MICs ranging from 0.1 to >10 μ g/mL). 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.

ABELCET® is active in animal models against *Aspergillus fumigatus*, *Candida albicans*, *C. guilliermondii*, *C. stellatoidea*, and *C. tropicalis*, *Cryptococcus* sp., *Coccidioidomycetes* sp., *Histoplasma* sp., and *Blastomyces* sp. in which end-points were clearance of microorganisms from target organ(s) and/or prolonged survival of infected animals.

Drug Resistance

Fungal species with decreased susceptibility to amphotericin B have been isolated after serial passage in culture media containing the drug, and from some patients receiving prolonged therapy. Although the relevance of drug resistance to clinical outcome has not been established, fungal species which are resistant to amphotericin B may also be resistant to ABELCET®.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The assay used to measure amphotericin B in the blood after the administration of ABELCET® does not distinguish amphotericin B that is complexed with the phospholipids of ABELCET® from amphotericin B that is uncomplexed.

The pharmacokinetics of amphotericin B after the administration of ABELCET® are nonlinear. Volume of distribution and clearance from blood increase with increasing dose of ABELCET®, resulting in less than proportional increases in blood concentrations of amphotericin B over a dose range of 0.6-5 mg/kg/day. The pharmacokinetics of amphotericin B in whole blood after the administration of ABELCET® and amphotericin B desoxycholate are:

Pharmacokinetic Parameters of Amphotericin B in Whole Blood in Patients Administered Multiple Doses of ABELCET® or Amphotericin B Desoxycholate		
Pharmacokinetic Parameter	ABELCET® 5 mg/kg/day for 5-7 days Mean \pm SD	Amphotericin B 0.6 mg/kg/day for 42 days ^a Mean \pm SD
Peak Concentration (μ g/mL)	1.7 \pm 0.8 (n=10) ^b	1.1 \pm 0.2 (n=5)
Concentration at End of Dosing Interval (μ g/mL)	0.6 \pm 0.3 (n=10) ^b	0.4 \pm 0.2 (n=5)
Area Under Blood Concentration-Time Curve (AUC _{0-24h}) (μ g·h/mL)	14 \pm 7 (n=14) ^{b,c}	17.1 \pm 5 (n=5)
Clearance (mL/h·kg)	436 \pm 188.5 (n=14) ^{b,c}	38 \pm 15 (n=5)
Apparent Volume of Distribution (V _{d,area}) (L/kg)	131 \pm 57.7 (n=8) ^e	5 \pm 2.8 (n=5)
Terminal Elimination Half-Life (h)	173.4 \pm 78 (n=8) ^e	91.1 \pm 40.9 (n=5)
Amount Excreted in Urine Over 24 h After Last Dose (% of dose) ^d	0.9 \pm 0.4 (n=8) ^e	9.6 \pm 2.5 (n=8)

^a Data from patients with mucocutaneous leishmaniasis. Infusion rate was 0.25 mg/kg/h.

^b Data from studies in patients with cytologically proven cancer being treated with chemotherapy or neutropenic patients with presumed or proven fungal infection. Infusion rate was 2.5 mg/kg/h.

^c Data from patients with mucocutaneous leishmaniasis. Infusion rate was 4 mg/kg/h.

^d Percentage of dose excreted in 24 hours after last dose.

The large volume of distribution and high clearance from blood of amphotericin B after the administration of ABELCET® probably reflect uptake by tissues. The long terminal elimination half-life probably reflects a slow redistribution from tissues. Although amphotericin B is excreted slowly, there is little accumulation in the blood after repeated dosing. AUC of amphotericin B increased approximately 34% from day 1 after the administration of ABELCET® 5 mg/kg/day for 7 days. The effect of gender or ethnicity on the pharmacokinetics of ABELCET® has not been studied.

Tissue concentrations of amphotericin B have been obtained at autopsy from one heart transplant patient who received three doses of ABELCET® at 5.3 mg/kg/day:

Concentration in Human Tissues	
Organ	Amphotericin B Tissue Concentration (μ g/g)
Spleen	290
Lung	222
Liver	196
Lymph Node	7.6
Kidney	6.9
Heart	5
Brain	1.6

This pattern of distribution is consistent with that observed in preclinical studies in dogs in which greatest concentrations of amphotericin B after ABELCET® administration were observed in the liver, spleen, and lung; however, the relationship of tissue concentrations of amphotericin B to its biological activity when administered as ABELCET® is unknown.

Special Populations

Hepatic Impairment: The effect of hepatic impairment on the disposition of ABELCET® is not known.

Renal Impairment: The effect of renal impairment on the disposition of ABELCET® is not known. The effect of dialysis on the elimination of ABELCET® has not been studied; however, amphotericin B is not removed by hemodialysis when administered as amphotericin B desoxycholate.

Pediatric and Elderly Patients: The pharmacokinetics and pharmacodynamics of pediatric patients (\leq 16 years of age) and elderly patients (\geq 65 years of age) have not been studied.

INDICATIONS AND USAGE

ABELCET® is indicated for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy. This is based on open-label treatment of patients judged by their physicians to be intolerant to or failing conventional amphotericin B therapy (See DESCRIPTION OF CLINICAL STUDIES).

DESCRIPTION OF CLINICAL STUDIES

Fungal Infections

Data from 473 patients were pooled from three open-label studies in which ABELCET® was provided for the treatment of patients with invasive fungal infections who were judged by their physicians to be refractory to or intolerant of conventional amphotericin B, or who had preexisting nephrotoxicity. Results of these studies demonstrated effectiveness of ABELCET® in the treatment of invasive fungal infections as a second line therapy.

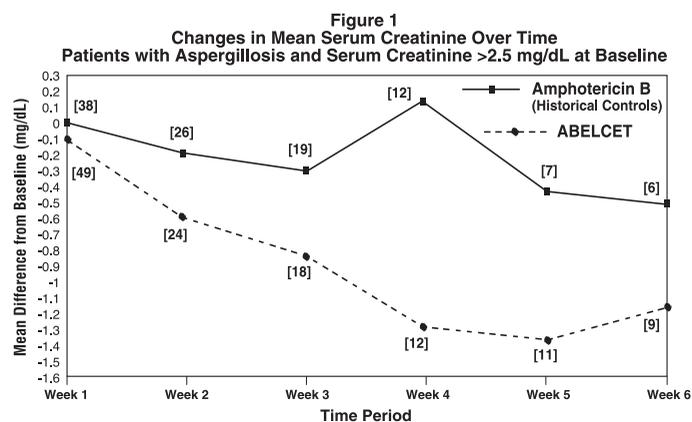
Patients were defined by their individual physician as being refractory to or failing conventional amphotericin B therapy based on overall clinical judgement after receiving a minimum total dose of 500 mg of amphotericin B. Nephrotoxicity was defined as a serum creatinine that had increased to >2.5 mg/dL in adults and >1.5 mg/dL in pediatric patients, or a creatinine clearance of <25 mL/min while receiving conventional amphotericin B therapy.

Of the 473 patients, four were enrolled more than once; each enrollment contributed separately to the denominator. The median age was 39 years (range of <1 to 93 years); 307 patients were male and 166 female. Patients were Caucasian (381, 81%), African-American (41, 9%), Hispanic (27, 6%), Asian (10, 2%), and various other races (14, 3%). The median baseline neutrophil count was 4,000 PMN/mm³; of these, 101 (21%) had a baseline neutrophil count <500/mm³.

Two-hundred eighty-two patients of the 473 patients were considered evaluable for response to therapy; the other 191 patients were excluded on the basis of unconfirmed diagnosis, confounding factors, concomitant systemic antifungal therapy, or receiving 4 doses or less of ABELCET®. For evaluable patients, the following fungal infections were treated (n=282): aspergillosis (n=111), candidiasis (n=87), zygomycosis (n=25), cryptococcosis (n=16), and fusariosis (n=11). There were fewer than 10 evaluable patients for each of several other fungal species treated.

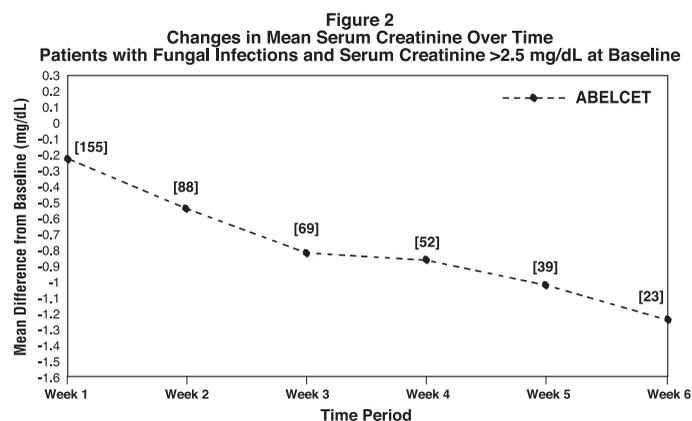
For each type of fungal infection listed above there were some patients successfully treated. However, in the absence of controlled studies it is unknown how response would have compared to either continuing conventional amphotericin B therapy or the use of alternative antifungal agents.

Renal Function: Patients with aspergillosis who initiated treatment with ABELCET® when serum creatinine was above 2.5 mg/dL experienced a decline in serum creatinine during treatment (Figure 1). Serum creatinine levels were also lower during treatment with ABELCET® when compared to the serum creatinine levels of patients treated with conventional amphotericin B in a retrospective historical control study. Meaningful statistical testing of the differences between these two groups is precluded since these data were obtained from two separate studies.



[] = Number of patients at each time point.

Note: These curves do not represent the clinical course of a given patient, but that of an open-label cohort of patients.



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In a randomized study of ABELCET® for the treatment of invasive candidiasis in patients with normal baseline renal function, the incidence of nephrotoxicity was significantly less for ABELCET® at a dose of 5 mg/kg/day than for conventional amphotericin B at a dose of 0.7 mg/kg/day.

Despite generally less nephrotoxicity of ABELCET® observed at a dose of 5 mg/kg/day compared with conventional amphotericin B therapy at a dose range of 0.6-1 mg/kg/day, dose-limiting renal toxicity may still be observed with ABELCET®. Renal toxicity of doses greater than 5 mg/kg/day of ABELCET® has not been formally studied.

CONTRAINDICATIONS

ABELCET® is contraindicated in patients who have shown hypersensitivity to amphotericin B or any other component in the formulation.

WARNINGS

Anaphylaxis has been reported with amphotericin B desoxycholate and other amphotericin B-containing drugs. Anaphylaxis has been reported with ABELCET® with an incidence rate of <0.1%. If severe respiratory distress occurs, the infusion should be immediately discontinued. The patient should not receive further infusions of ABELCET®.

PRECAUTIONS

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

Acute reactions including fever and chills may occur 1 to 2 hours after starting an intravenous infusion of ABELCET®. These reactions are usually more common with the first few doses of ABELCET® and generally diminish with subsequent doses. Infusion has been rarely associated with hypotension, bronchospasm, arrhythmias, and shock.

Laboratory Tests: Serum creatinine should be monitored frequently during ABELCET® therapy (see ADVERSE REACTIONS). It is also advisable to regularly monitor liver function, serum electrolytes (particularly magnesium and potassium), and complete blood counts.

Drug Interactions: No formal clinical studies of drug interactions have been conducted with ABELCET®. However, when administered concomitantly, the following drugs are known to interact with amphotericin B; therefore, the following drugs may interact with ABELCET®:

Antineoplastic agents: Concurrent use of antineoplastic agents and amphotericin B may enhance the potential for renal toxicity, bronchospasm, and hypotension. Antineoplastic agents should be given concomitantly with ABELCET® with great caution.

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 used concomitantly with ABELCET®, serum electrolytes and cardiac function should be closely monitored.

Cyclosporin A: Data from a prospective study of prophylactic ABELCET® in 22 patients undergoing bone marrow transplantation suggested that concurrent initiation of cyclosporin A and ABELCET® within several days of bone marrow ablation may be associated with increased nephrotoxicity.

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

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

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.

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

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

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

Zidovudine: Increased myelotoxicity and nephrotoxicity were observed in dogs when either ABELCET® (at doses 0.16 or 0.5 times the recommended human dose) or amphotericin B desoxycholate (at 0.5 times the recommended human dose) were administered concomitantly with zidovudine for 30 days. If zidovudine is used concomitantly with ABELCET®, renal and hematologic function should be closely monitored.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of ABELCET®. The following *in vitro* (with and without metabolic activation) and *in vivo* studies to assess ABELCET® for mutagenic potential were conducted: bacterial reverse mutation assay, mouse lymphoma forward mutation assay, chromosomal aberration assay in CHO cells, and *in vivo* mouse micronucleus assay. ABELCET® was found to be without mutagenic effects in all assay systems. Studies demonstrated that ABELCET® had no impact on fertility in male and female rats at doses up to 0.32 times the recommended human dose (based on body surface area considerations).

Pregnancy: There are no reports of pregnant women having been treated with ABELCET®. Teratogenic Effects. Pregnancy Category B: Reproductive studies in rats and rabbits at doses of ABELCET® up to 0.64 times the human dose revealed no harm to the fetus. Because animal reproductive studies are not always predictive of human response, and adequate and well-controlled studies have not been conducted in pregnant women, ABELCET® should be used during pregnancy only after taking into account the importance of the drug to the mother.

Nursing Mothers: It is not known whether ABELCET® is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in breast-fed infants from ABELCET®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: One hundred eleven children (2 were enrolled twice and counted as separate patients), age 16 years and under, of whom 11 were less than 1 year, have been treated with ABELCET® at 5 mg/kg/day in two open-label studies and one small, prospective, single-arm study. In one single-center study, 5 children with hepatosplenic candidiasis were effectively treated with 2.5 mg/kg/day of ABELCET®. No serious unexpected adverse events have been reported.

Geriatric Use: Forty-nine elderly patients, age 65 years or over, have been treated with ABELCET® at 5 mg/kg/day in two open-label studies and one small, prospective, single-arm study. No serious unexpected adverse events have been reported.

ADVERSE REACTIONS

The total safety data base is composed of 921 patients treated with ABELCET® (5 patients were enrolled twice and counted as separate patients), of whom 775 were treated with 5 mg/kg/day. Of these 775 patients, 194 patients were treated in four comparative studies; 25 were treated in open-label, non-comparative studies; and 556 patients were treated in an open-label, emergency-use program. Most had underlying hematologic neoplasms, and many were receiving multiple concomitant medications. Of the 556 patients treated with ABELCET®, 9% discontinued treatment due to adverse events regardless of presumed relationship to study drug.

In general, the adverse events most commonly reported with ABELCET® were transient chills and/or fever during infusion of the drug.

Adverse Events ^a with an Incidence of ≥3% (N=556)	
Adverse Event	Percentage (%) of Patients
Chills	18
Fever	14
Increased Serum Creatinine	11
Multiple Organ Failure	11
Nausea	9
Hypotension	8
Respiratory Failure	8
Vomiting	8
Dyspnea	7
Sepsis	7
Diarrhea	6
Headache	6
Cardiac Arrest	6
Hypertension	5
Hypokalemia	5
Infection	5
Kidney Failure	5
Pain	5
Thrombocytopenia	5
Abdominal Pain	4
Anemia	4
Hyperbilirubinemia	4
Gastrointestinal Hemorrhage	4
Leukopenia	4
Rash	4
Respiratory Disorder	4
Chest Pain	3
Nausea and Vomiting	3

^aThe causal association between these adverse events and ABELCET® is uncertain.

The following adverse events have also been reported in patients using ABELCET® in open-label, uncontrolled clinical studies. The causal association between these adverse events and ABELCET® is uncertain.

Body as a whole: malaise, weight loss, deafness, injection site reaction including inflammation

Allergic: bronchospasm, wheezing, asthma, anaphylactoid and other allergic reactions

Cardiopulmonary: cardiac failure, pulmonary edema, shock, myocardial infarction, hemoptysis, tachypnea, thrombophlebitis, pulmonary embolus, cardiomyopathy, pleural effusion, arrhythmias including ventricular fibrillation

Dermatological: maculopapular rash, pruritus, exfoliative dermatitis, erythema multiforme

Gastrointestinal: acute liver failure, hepatitis, jaundice, melena, anorexia, dyspepsia, cramping, epigastric pain, veno-occlusive liver disease, diarrhea, hepatomegaly, cholangitis, cholecystitis

Hematologic: coagulation defects, leukocytosis, blood dyscrasias including eosinophilia

Musculoskeletal: myasthenia, including bone, muscle, and joint pains

Neurologic: convulsions, tinnitus, visual impairment, hearing loss, peripheral neuropathy, transient vertigo, diplopia, encephalopathy, cerebral vascular accident, extrapyramidal syndrome and other neurologic symptoms

Urogenital: oliguria, decreased renal function, anuria, renal tubular acidosis, impotence, dysuria

Serum electrolyte abnormalities: hypomagnesemia, hyperkalemia, hypocalcemia, hypercalcemia

Liver function test abnormalities: increased AST, ALT, alkaline phosphatase, LDH

Renal function test abnormalities: increased BUN

Other test abnormalities: acidosis, hyperamylasemia, hypoglycemia, hyperglycemia, hyperuricemia, hypophosphatemia

To report SUSPECTED ADVERSE REACTIONS, contact Sigma-Tau Pharmaceuticals, Inc. at 1-888-393-4584 or by email at drugsafety@sigmatau.com or contact the FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch.

OVERDOSAGE

Amphotericin B desoxycholate overdose has been reported to result in cardio-respiratory arrest. Fifteen patients have been reported to have received one or more doses of ABELCET® between 7-13 mg/kg. None of these patients had a serious acute reaction to ABELCET®. If an overdose is suspected, discontinue therapy, monitor the patient's clinical status, and administer supportive therapy as required. ABELCET® is not hemodialyzable.

DOSAGE AND ADMINISTRATION

The recommended daily dosage for adults and children is 5 mg/kg given as a single infusion. ABELCET® should be administered by intravenous infusion at a rate of 2.5 mg/kg/h. If the infusion time exceeds 2 hours, mix the contents by shaking the infusion bag every 2 hours.

Renal toxicity of ABELCET®, as measured by serum creatinine levels, has been shown to be dose dependent. Decisions about dose adjustments should be made only after taking into account the overall clinical condition of the patient.

Preparation of Admixture for Infusion: Shake the vial gently until there is no evidence of any yellow sediment at the bottom. Withdraw the appropriate dose of ABELCET® from the required number of vials into one or more sterile syringes using an 18-gauge needle. Remove the needle from each syringe filled with ABELCET® and replace with the 5-micron filter needle supplied with each vial. Each filter needle may be used to filter the contents of up to four 100 mg vials. Insert the filter needle of the syringe into an IV bag containing 5% Dextrose Injection USP, and empty the contents of the syringe into the bag. The final infusion concentration should be 1 mg/mL. For pediatric patients and patients with cardiovascular disease the drug may be diluted with 5% Dextrose Injection to a final infusion concentration of 2 mg/mL. Before infusion, shake the bag until the contents are thoroughly mixed. Do not use the admixture after dilution with 5% Dextrose Injection if there is any evidence of foreign matter. Vials are for single use. Unused material should be discarded. Aseptic technique must be strictly observed throughout handling of ABELCET®, since no bacteriostatic agent or preservative is present.

DO NOT DILUTE WITH SALINE SOLUTIONS OR MIX WITH OTHER DRUGS OR ELECTROLYTES as the compatibility of ABELCET® with these materials has not been established. An existing intravenous line should be flushed with 5% Dextrose Injection before infusion of ABELCET®, or a separate infusion line should be used. **DO NOT USE AN IN-LINE FILTER.**

The diluted ready-for-use admixture is stable for up to 48 hours at 2° to 8°C (36° to 46°F) and an additional 6 hours at room temperature.

HOW SUPPLIED

Single-use vials along with 5-micron filter needles are individually packaged.

100 mg of ABELCET® in 20 mL of suspension NDC 57665-101-41

STORAGE

Prior to admixture, ABELCET® should be stored at 2° to 8°C (36° to 46°F) and protected from exposure to light. Do not freeze. ABELCET® should be retained in the carton until time of use.

The admixed ABELCET® and 5% Dextrose Injection may be stored for up to 48 hours at 2° to 8°C (36° to 46°F) and an additional 6 hours at room temperature. Do not freeze. Any unused material should be discarded.

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