PRODUCT MONOGRAPH

PrABELCET®

(Amphotericin B Lipid Complex Injection)

5 mg Amphotericin B/mL: 20 mL Vial

Injectable Suspension

Antifungal

Sigma-Tau Pharmaceuticals, Inc.
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Date of Preparation: March 29, 2010
Date of Revision:

Control#: 137174

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THERAPEUTIC CLASSIFICATION
Antifungal

ACTION AND CLINICAL PHARMACOLOGY

The active component in Amphotericin B Lipid Complex Injection is amphotericin B which acts by binding to sterols in the cell membrane of susceptible fungi, with a resultant change in 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.

Pharmacokinetics: 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 shown in Table 1.

Table 1. 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 ± SD**	**Amphotericin B 0.6 mg/kg/day for 42 days[a] Mean ± SD**
Peak Concentration (µg/mL)	1.7 ± 0.8 (n=10)[b]	1.1 ± 0.2 (n=5)
Concentration at End of Dosing Interval (µg/mL)	0.6 ± 0.3 (n=10)[b]	0.4 ± 0.2 (n=5)
Area Under Blood Concentration-Time Curve (AUC_{0-24h}) (µg*h/mL)	14 ± 7 (n=14)[b,c]	17.1 ± 5 (n=5)
Clearance (mL/h*kg)	436 ± 188.5 (n=14)[b,c]	38 ± 15 (n=5)
Apparent Volume of Distribution (Vd_{area}) (L/kg)	131 ± 57.7 (n=8)[c]	5 ± 2.8 (n=5)
Terminal Elimination Half-Life (h)	173.4 ± 78 (n=8)[c]	91.1 ± 40.9 (n=5)
Amount Excreted in Urine Over 24 h After Last Dose (% of dose)[d]	0.9 ± 0.4 (n=8)[c]	9.6 ± 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 value from the 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 Amphotericin B Lipid Complex Injection 5 mg/kg/day for 7 days. The effect of gender or ethnicity on the pharmacokinetics of Amphotericin B Lipid Complex Injection has not been studied.

Tissue concentrations of amphotericin B were obtained at autopsy from one heart transplant patient who received three doses of Amphotericin B Lipid Complex Injection at 5.3 mg/kg/day. The results are shown in Table 2.

Table 2. Amphotericin B Tissue Concentrations	
Organ	**Amphotericin B Tissue Concentration (µg/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 Amphotericin B Lipid Complex Injection is unknown.

INDICATIONS AND CLINICAL USE

ABELCET® (Amphotericin B Lipid Complex Injection) 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 PHARMACOLOGY: Clinical Studies). ABELCET® has been used in 162 patients who had developed nephrotoxicity while receiving amphotericin B therapy and in a small number of patients who had pre-existing renal insufficiency (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

ABELCET® (Amphotericin B Lipid Complex Injection) 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 rarely reported with ABELCET® (Amphotericin B Lipid Complex Injection) with an incidence of <0.1%. Facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactoid reaction. 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 intravenously 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.

Renal toxicity of doses greater than 5 mg/kg/day of ABELCET® has not been formally studied. 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®.

Use in the Elderly: 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 drug related adverse events have been reported that might not be expected from the general patient population.

Use in Children: 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. No serious drug related adverse events have been reported that might not be expected from the general patient population.

Use in Pregnancy: There are no reports of pregnant women having been treated with ABELCET®. 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.

Patients with Special Diseases or Conditions

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

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

Dependence Liability: ABELCET® is not addictive.

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.

ADVERSE REACTIONS

The total safety data base is composed of 921 patients treated with ABELCET® (Amphotericin B Lipid Complex Injection, (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. These 556 patients were treated for their invasive fungal infections, and were refractory to or intolerant of conventional amphotericin B therapy. Most had underlying hematologic neoplasms, and many were receiving multiple concomitant medications. Of the 556 patients treated with ABELCET®, 9% of ABELCET® patients discontinued treatment due to adverse events, regardless of presumed relationship to drug.

In general, the adverse events most commonly reported with ABELCET® were transient chills and fever during infusion of the drug. Table 3 lists the most frequently reported adverse events.

Table 3. Adverse Events[a] with Incidence Rates ≥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
Heart Arrest	6
Hypertension	5
Hypokalemia	5
Infection	5
Kidney Failure	5
Pain	5
Thrombocytopenia	5
Abdominal Pain	4
Anemia	4
Bilirubinemia	4
Gastrointestinal Hemorrhage	4
Leukopenia	4

Table 3. Adverse Events[a] with Incidence Rates ≥3% (N=556)	
Adverse Event	**Percentage (%) of Patients**
Rash	4
Respiratory Disorder	4
Chest Pain	3
Nausea and Vomiting	3

[a]The causal association between 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: anorexia, 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, tremors, transient vertigo, diplopia, encephalopathy, cerebral vascular accident, extrapyramidal syndrome and other neurologic symptoms

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

Altered Laboratory Findings

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Amphotericin B desoxycholate overdose has been reported to result in cardio-respiratory arrest. Twelve patients have been reported to have received two 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 (See PRECAUTIONS) is 5 mg/kg given as a single infusion. ABELCET® (Amphotericin B Lipid Complex Injection) should be administered by intravenous infusion at a rate of 2.5 mg/kg/h. If the infusion time exceeds 2 hours, resuspend the contents by shaking the infusion bag every 2 hours. Facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactoid reaction.

The median and mean duration of ABELCET® treatment was 22 days and 33 days, respectively. ABELCET® has been administered for as long as 17 months, and cumulative doses have been as high as 56.6 g.

RENAL IMPAIRMENT: Renal toxicity of ABELCET®, as measured by serum creatinine levels, has been shown to be dose dependent. There are no firm guidelines for dose adjustment based on laboratory test results and decisions about dose adjustments should be

made only after taking into account the overall clinical condition of the patient (See PRECAUTIONS and SYMPTOMS AND TREATMENT OF OVERDOSAGE). Some patients with elevated serum creatinine levels have improved renal function while on Abelcet treatment (See CLINICAL STUDIES).

HEPATIC IMPAIRMENT: No dose adjustment is required for patients with hepatic impairment.

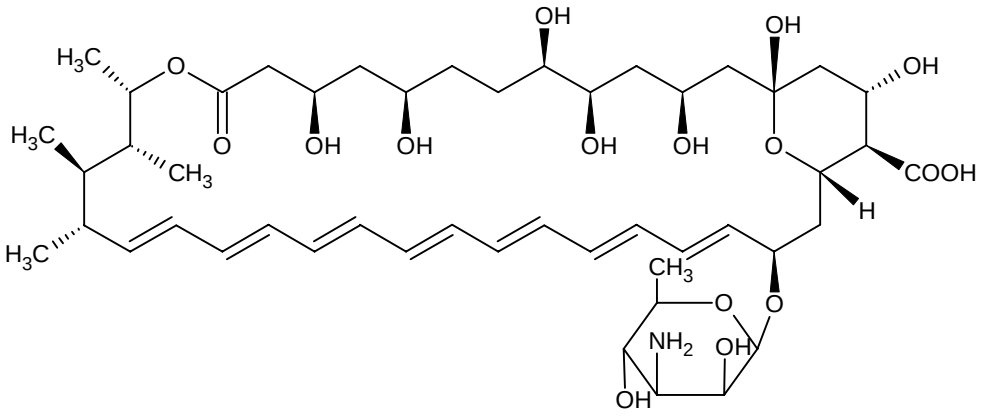
PHARMACEUTICAL INFORMATION

Drug Substance:

***Proper Name*:** Amphotericin B

***Chemical Name*:** [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

Structural Formula:



Molecular Weight: 924.09

Molecular Formula: $C_{47}H_{73}NO_{17}$

Description: Amphotericin B is a polyene, antifungal antibiotic produced from a strain of *Streptomyces nodosus*. Amphotericin B is effective against a broad variety of fungi and yeasts. Amphotericin B is a deep yellow to golden-orange, granular powder which is described as odorless to practically odorless. There is no evidence of melting in amphotericin B at temperatures up to 250ºC, at which temperature it has already decomposed. Amphotericin B is amphoteric with both polar and nonpolar portions. It dissolves poorly in most pure solvents; exceptions are dimethyl sulfoxide (30 to 40 mg/mL) and dimethyl formamide (2 to 4 mg/mL).

Composition: 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.

ABELCET® (Amphotericin B Lipid Complex Injection) is a sterile, pyrogen-free suspension for intravenous infusion. While ABELCET® consists of amphotericin B combined with two phospholipids in roughly a 1:1 drug-to-lipid weight ratio, the stoichiometry of the molecular complex that forms between amphotericin B and lipid is near a 1:1 drug-to-lipid molar ratio. ABELCET® is yellow and opaque in appearance, with a pH of 5-7.

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, 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	

Stability and Storage Conditions: Prior to admixture, ABELCET® should be stored at 2º to 8ºC (36º to 46ºF) 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 2º to 8ºC (36º to 46ºF) and an additional 6 hours at room temperature. Do not freeze. Any unused material should be discarded.

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 to 2 mg/mL. 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 2º to 8ºC (36º to 46ºF) and an additional 6 hours at room temperature.

AVAILABILITY OF DOSAGE FORMS

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

100 mg of ABELCET® in 20 mL of suspension.