AUSTRALIAN PI – ABELCET® (AMPHOTERICIN LIPID COMPLEX) INJECTION

1 NAME OF THE MEDICINE

Amphotericin B (amphotericin).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ABELCET is supplied as a 20 mL suspension in a vial. Each vial contains the equivalent of 100 mg of amphotericin B.

For the full list of excipients, see Section 6.1 "List of excipients."

3 PHARMACEUTICAL FORM

ABELCET is a sterile, pyrogen-free suspension in isotonic saline. It consists of amphotericin, of which amphotericin B is the major component, in a complex with phospholipids. Amphotericin is a macrocyclic, polyene, broad-spectrum antifungal antibiotic produced by *Streptomyces nodosus*. The lipophilic moiety of amphotericin B allows molecules of the drug to be complexed in a ribbon-like structure with the phospholipids.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ABELCET is indicated for the treatment of invasive fungal disease caused by organisms susceptible to amphotericin B (see Section 5.1 Pharmacodynamic properties, Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

ABELCET is a sterile, pyrogen-free suspension to be diluted for intravenous infusion only.

Vials are for single use in one patient on one occasion only. Aseptic technique must be strictly observed throughout handling of ABELCET since no bacteriostatic agent or preservative is present.

Dosage

The recommended daily dose is 5.0 mg/kg given as a single infusion. Use of other doses has not been supported by adequate information.

An initial test dose of 1.0 mg should be infused intravenously over 15 minutes. Facilities for resuscitation should be readily at hand.

ABELCET should be administered by intravenous infusion at a rate of 2.5 mg/kg/h. Before infusion, the suspension must be filtered using the filter needle provided (to remove any large particles present) and then diluted with 5.0% glucose injection, according to the Section below titled, "Preparation of the Suspension for Infusion."

An in-line filter may be used for intravenous infusion of ABELCET. The mean pore diameter of the filter should not be less than 5.0 microns. For severe systemic infections, treatment duration is typically at least 14 days. ABELCET has been administered for as long as 11 months, and cumulative doses have been as high as 56.6 g without significant toxicity.

Preparation of the Suspension for Infusion

1. Allow the suspension to come to room temperature. Shake gently until there is no evidence of any yellow sediment at the bottom of the vial.
2. Withdraw the appropriate dose of ABELCET from the required number of vials into a sterile syringe using a 17 to 19 gauge needle.
3. Remove the needle from the syringe filled with ABELCET and replace with the 5 micron high flow filter needle provided with each vial.
4. Insert the filter needle of the syringe into an IV bag containing 5.0% glucose solution. The content of the syringe should then be emptied into the bag by manual pressure or via an infusion pump.

Each needle provided with a filter may only be used to filter the contents of one bottle and another needle must be used with each new bottle. The final infusion concentration should be 1 mg/mL.

Discard after dilution if there is any evidence of foreign material in the solution. The infusion is best administered by means of an infusion pump.

DO NOT DILUTE WITH SALINE SOLUTIONS OR MIX WITH OTHER DRUGS OR ELECTROLYTES. The compatibility of ABELCET with these materials has not been established. An existing intravenous line should be flushed with 5.0% glucose injection before infusion of ABELCET, or a separate infusion line should be used.

To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours. Following storage in IV bags, the ready for use ABELCET suspension must be vigorously agitated prior to use.

Dosage Adjustments

Use in patients with renal impairment

Systemic fungal infections in patients with renal disease have been treated with Abelcet at doses comparable to the recommended dose on a bodyweight basis. See Section 4.4 “Special warnings and precautions for use.”)

Use in elderly patients

Systemic fungal infections have been treated in elderly patients (65 years or older) at doses comparable to the recommended dose on a bodyweight basis. (See Section 4.4 “Special warnings and precautions for use.”)

Paediatric population

Systemic fungal infections have been treated in children ranging from 1 month to 16 years of age. The doses used are comparable to the doses recommended for adults on a bodyweight basis. (See Section 4.4 “Special warnings and precautions for use.”)

4.3 CONTRAINDICATIONS

ABELCET is contraindicated in patients with known hypersensitivity to any of its constituents unless, in the opinion of the physician, the advantages of using ABELCET outweigh the risk of hypersensitivity.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Treatment with ABELCET requires hospitalisation and supervision by a physician.

Adverse reactions similar to those associated with conventional amphotericin B may occur with ABELCET. Patients should be monitored for any type of adverse reaction associated with conventional amphotericin B. Particular attention should be paid to patients receiving nephrotoxic drugs concomitantly with ABELCET. Renal function should be monitored closely in these patients.

Anaphylactoid reactions and asthma have been reported in patients given ABELCET. Facilities for cardiopulmonary resuscitation should be readily at hand when ABELCET is being administered. *If severe respiratory distress and/or anaphylaxis occur with the infusion of ABELCET, the infusion should be immediately discontinued. The patient should not receive further infusions of ABELCET.*

Infusion Hypersensitivity Reactions

Infusion related reactions (such as chills and pyrexia) recorded following the administration of ABELCET have generally been mild or moderate and have mainly been recorded during the first 2 days of administration (see Section 4.8 “ADVERSE EFFECTS”). These reactions normally abate after a few days of treatment and consideration of precautionary measures for the prevention or treatment of these reactions should be given to patients who received ABELCET therapy. Routine doses of acetylsalicylic acid, antipyretics (e.g. paracetamol), antihistaminic and anti-emetic treatments have been reported as successful in their prevention or treatment.

Systemic fungal infections

Do not use ABELCET for treatment of common or superficial, clinically unapparent fungal infections that are detectable only by positive skin or serologic tests.

Use in Renal Dialysis Patients

ABELCET should be administered to renal dialysis patients only after the completion of dialysis. Serum potassium and magnesium levels should be monitored regularly. ABELCET may be given to patients with renal failure at the recommended adult dose.

Use in renal impairment

Since ABELCET is a potentially nephrotoxic drug, monitoring of renal function should be performed before initiating treatment in patients with pre-existing renal disease or who have already experienced renal failure, and regularly during therapy. In patients with serious systemic fungal infections and contraindications to conventional amphotericin B who were treated with ABELCET renal function remained stable in 50.5% of patients, improved in 21.8% and declined in 24.4% after 6 weeks of treatment. In the subpopulation of cases with baseline serum creatinine levels greater than 221 µmol/L, the mean serum creatinine decreased from 339 µmol/L at the start of treatment to 229 µmol/L after 6 weeks of treatment. Renal dysfunction that developed during treatment with conventional amphotericin B has been shown to stabilise or improve frequently during subsequent ABELCET treatment.

Use in the elderly

Systemic fungal infections in elderly patients have been treated successfully with ABELCET.

The adverse reaction profile is similar to that seen in adults less than 65 years of age, with the exception of increases in serum creatinine and dyspnoea for both ABELCET and conventional amphotericin B which were reported with a greater frequency in patients ≥65 years of age.

The dose to be given should be calculated using the same dose per kg of weight as is used to calculate the recommended dose.

Paediatric use

Systemic fungal infections in children have been treated successfully with ABELCET. The dose to be given should be calculated using the same dose per kg of weight as is used to calculate the recommended adult dose.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interaction of ABELCET with other drugs has not been studied to date. However, when administered concomitantly, the following drugs are known to interact with conventional amphotericin B; therefore the following treatments may interact with ABELCET.

Nephrotoxic drugs

ABELCET is a potentially nephrotoxic drug and monitoring of renal function is recommended in patients receiving nephrotoxic drugs concomitantly.

Leukocyte transfusions

Acute pulmonary toxicity has been reported in patients receiving intravenous conventional amphotericin B and leukocyte transfusions. Conventional amphotericin B and leukocyte should not be given concomitantly.

Zidovudine

In dogs, exacerbated myelotoxicity and nephrotoxicity were observed when ABELCET (1.5 or 5.0 mg/kg/day) was administered concomitantly with zidovudine for 30 days. If concomitant treatment with both agents is required, renal and haematologic function should be closely monitored.

Cyclosporin

Preliminary data suggest that patients receiving ABELCET concomitantly with high dose cyclosporin experience an increase in serum creatinine. The data also indicate that the increase in serum creatinine is caused by cyclosporin and not ABELCET. Until further information is available, renal function should be monitored closely in patients who receive concomitant treatment with both drugs.

Other drugs

Conventional amphotericin B has been reported to interact with antineoplastic agents, corticosteroids and corticotrophin (ACTH), digitalis glycosides, flucytosine and skeletal muscle relaxants. Caution should be exercised during concomitant use with ABELCET.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no effect on fertility in rats dosed with ABELCET at up to 10 mg/kg/day amphotericin B (0.32 times the recommended human dose, based on body surface area).

Use in pregnancy – Pregnancy Category B3

Conventional amphotericin B has been used successfully to treat systemic fungal infections in pregnant women with no obvious effect on the foetus, but only a small number of cases have been reported. Reproductive studies of ABELCET in rats showed no evidence of embryotoxicity, foetotoxicity or teratogenicity at plasma drug exposures similar to those expected therapeutically. However, in rabbits, a dose-ranging teratogenicity study, but not the subsequent full study, indicated that ABELCET may have embryotoxic and foetotoxic effects at estimated plasma exposures (based on C_{max}) below those expected in patients. As uncertainty remains as to whether or not ABELCET can affect the developing embryo/foetus, the drug should be administered to pregnant women only for life-threatening disease when the likely benefit exceeds the risk to mother and foetus.

Use in lactation.

It is not known whether ABELCET is excreted in human milk, and there have been no relevant studies in animals. As many drugs are excreted in human milk and can be harmful to the baby, treatment of lactating women with ABELCET is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of Abelcet on the ability to drive and/or use machines have not been investigated. Some of the undesirable effects of Abelcet presented below may impact the ability to drive and use machines. However, the clinical condition of most patients treated with Abelcet precludes driving vehicles or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The most common clinical adverse reactions have been chills, increased creatinine, pyrexia, hypokalaemia, nausea, vomiting and fever. Premedication (e.g. paracetamol) may be administered for the prevention of infusion related adverse reactions.

Adverse experiences reported among patients with invasive candidiasis treated with ABELCET (n=153) or amphotericin B (n=78) in a comparative clinical trial are shown in the table below. Included are all adverse events occurring with an incidence rate of greater than or equal to 5%.

Table 1: Adverse experiences reported among patients with invasive candidiasis treated with ABELCET or amphotericin B.

Study AI800-017 **Invasive Candidiasis** **Adverse Events (Regardless of Causality) Grouped by Body System** **with Incidence ≥ 5%**				
	ABELCET **5.0 mg/kg/day**		**Amphotericin B** **0.6 mg/kg/day**	
	Incidence ≥5%			
Body System/Adverse Events	n		n	
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Body as a Whole	116	(76)	57	(73)
Sepsis	38	(25)	14	(18)
Infection	32	(21)	19	(24)
Fever	30	(20)	13	(17)
Chills	19	(12)	3	(4)
Abdominal Pain	18	(12)	15	(19)
Pain	15	(10)	9	(12)
Generalised Oedema	12	(8)	9	(12)
Chest Pain	12	(8)	6	(8)
Headache	9	(6)	8	(10)

Study AI800-017 Invasive Candidiasis Adverse Events (Regardless of Causality) Grouped by Body System with Incidence ≥ 5%				
	ABELCET **5.0 mg/kg/day**		**Amphotericin B** **0.6 mg/kg/day**	
	Incidence ≥5%			
Body System/Adverse Events	n		n	
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Injection Site Reaction	9	(6)	5	(6)
Asthenia	8	(5)	5	(6)
Injection Site Hypersensitivity	2	(1)	6	(8)
Cardiovascular System	99	(65)	42	(54)
Hypotension	49	(32)	15	(19)
Tachycardia	25	(16)	6	(8)
Heart Arrest	15	(10)	13	(17)
Hypertension	13	(8)	8	(10)
Heart Failure	12	(8)	6	(8)
Atrial Fibrillation	10	(7)	4	(5)
Phlebitis	7	(5)	2	(3)
Supraventricular Tachycardia	7	(5)	2	(3)
Electrocardiogram Abnormal	5	(3)	8	(10)
Digestive System	92	(60)	50	(64)
Diarrhoea	26	(17)	12	(15)
Nausea	24	(16)	11	(14)
Vomiting	20	(13)	8	(10)
Nausea and Vomiting	8	(5)	7	(9)
Gastrointestinal Haemorrhage	10	(7)	3	(4)

Study AI800-017 Invasive Candidiasis Adverse Events (Regardless of Causality) Grouped by Body System with Incidence ≥ 5%				
	ABELCET **5.0 mg/kg/day**		**Amphotericin B** **0.6 mg/kg/day**	
	Incidence ≥5%			
Body System/Adverse Events	n		n	
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Constipation	9	(6)	8	(10)
Anorexia	8	(5)	0	
Liver Function Tests Abnormal	7	(5)	5	(6)
Haemic and Lymphatic System	57	(37)	40	(51)
Anaemia	26	(17)	14	(18)
Leukocytosis	15	(10)	12	(15)
Thrombocytopenia	12	(8)	5	(6)
Blood Dyscrasia	6	(4)	1	(1)
Thromboplastin Decreased	6	(4)	5	(6)
Leukopenia	5	(3)	7	(9)
Cyanosis	1	(1)	5	(6)
Metabolic and Nutritional Disorders	110	(72)	65	(83)
Creatinine Increased	51	(33)	35	(45)
Hypokalaemia	41	(27)	15	(19)
Urea Increased	29	(19)	20	(26)
Alkaline Phosphatase Increased	25	(16)	16	(21)
Hypomagnesaemia	18	(12)	8	(10)
Acidosis	15	(10)	6	(8)
Peripheral Oedema	15	(10)	9	(12)

Study AI800-017 **Invasive Candidiasis** **Adverse Events (Regardless of Causality) Grouped by Body System** **with Incidence ≥ 5%**				
	ABELCET **5.0 mg/kg/day**		**Amphotericin B** **0.6 mg/kg/day**	
	Incidence ≥5%			
Body System/Adverse Events	n		n	
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Bilirubinaemia	14	(9)	7	(9)
Hyperkalaemia	12	(8)	6	(8)
Hypoxia	11	(7)	1	(1)
Hyperglycaemia	9	(6)	5	(6)
Hypernatraemia	9	(6)	5	(6)
Hyperphosphataemia	8	(5)	6	(8)
Hyponatraemia	8	(5)	5	(6)
Hyperchloraemia	6	(4)	5	(6)
SGPT Increased	5	(3)	5	(6)
Hypoglycaemia	2	(1)	7	(9)
Nervous System	67	(44)	22	(28)
Confusion	16	(10)	4	(5)
Insomnia	12	(8)	5	(6)
Somnolence	12	(8)	5	(6)
Anxiety	11	(7)	3	(4)
Agitation	7	(5)	3	(4)
Respiratory System	99	(65)	56	(72)
Dyspnoea	37	(24)	26	(33)
Plural Effusion	24	(16)	5	(6)

Study AI800-017 **Invasive Candidiasis** **Adverse Events (Regardless of Causality) Grouped by Body System** **with Incidence ≥ 5%**				
	ABELCET **5.0 mg/kg/day**		**Amphotericin B** **0.6 mg/kg/day**	
	Incidence ≥5%			
Body System/Adverse Events	n		n	
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Lung Disorder	22	(14)	14	(18)
Respiratory Disorder	19	(12)	9	(12)
Pneumonia	15	(10)	7	(9)
Hyperventilation	13	(8)	9	(12)
Asthma	11	(7)	3	(4)
Lung Oedema	10	(7)	3	(4)
Haemoptysis	9	(6)	1	(1)
Respiratory Failure	9	(6)	9	(12)
Cough Increased	8	(5)	1	(1)
Pharyngitis	7	(5)	2	(3)
Apnoea	1	(1)	6	(8)
Skin & Appendages	41	(27)	25	(32)
Rash	12	(8)	13	(17)
Pruritus	7	(5)	2	(3)
Skin Ulcer	5	(3)	5	(6)
Urogenital System	72	(47)	40	(51)
Haematuria	29	(19)	16	(21)
Urinary Tract Infection	16	(10)	9	(12)
Pyuria	15	(10)	8	(10)

Study AI800-017 Invasive Candidiasis Adverse Events (Regardless of Causality) Grouped by Body System with Incidence ≥ 5%				
	ABELCET 5.0 mg/kg/day		Amphotericin B 0.6 mg/kg/day	
	Incidence ≥5%			
Body System/Adverse Events	n		n	
No. of Patients Treated	153	(%)	78	(%)
No. of Patients Who Reported AEs	149		78	
Oliguria	11	(7)	5	(6)
Kidney Function Abnormal	9	(6)	5	(6)
Kidney Failure	7	(5)	6	(8)
Urinary Tract Disorder	1	(1)	4	(5)

Post-marketing Data

The following additional post-marketing adverse reactions are listed below as MedDRA preferred terms by system organ class and frequency. Frequencies are defined as:

Very common (>1/10), Common (>1/100 to ≤1/10), Uncommon (>1/1000 and ≤1/100), Rare (>1/10,000 to ≤1/1,000), Very rare (≥1/10,000) and Not known (cannot be estimated from the available data).

Table 2: Tabulated listing of adverse effects reported by organ class.

System organ class	**Adverse reaction**	**Frequency**
Investigations		
	Blood creatinine increased	Very common
	Blood alkaline phosphatise increased, blood urea increased	Common
Cardiac disorders		
	Tachycardia, cardiac arrhythmias, hypotension	Common
	Shock, cardiac arrest	Uncommon
	arrhythmia, asystole, bradycardia, haemorrhage	Very rare
Blood and lymphatic system disorders		
	Thrombocytopenia	Common
	Pancytopenia	Very rare
Nervous system disorders		
	Headache, tremor	Common
	Convulsion, neuropathy	Uncommon
	Agitation, confusion, encephalopathy, stupor	Very rare
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea, asthma	Common
	Respiratory failure	Uncommon
	Hypoxia	Very rare
	Bronchospasm	Not known
Gastrointestinal disorders		
	Nausea, vomiting, abdominal pain	Common

	Gastrointestinal haemorrhage, liver function abnormal, peritonitis	Very rare
Musculoskeletal and connective tissue disorders		
	Myalgia	Uncommon
	Myoclonus	Very rare
Renal and urinary disorders		
	Renal impairment including renal failure	Common
	Anuria, incontinence	Very rare
	Hyposthenuria, Renal tubular acidosis, nephrogenic diabetes insipidus.	Not known
Skin and subcutaneous tissue disorders		
	Rash	Common
	Pruritis	Uncommon
	Dermatitis exfoliative	Not known
Metabolism and nutrition disorders		
	Hyperbilirubinaemia, hypokalaemia, Electrolyte imbalance including blood potassium increased, blood magnesium decreased	Common
	Hypoglycaemia, hyperammonaemia	Very rare
Vascular disorders		
	Hypertension, hypotension	Common
	Shock	Uncommon
General disorders and administration site conditions		
	Chills, pyrexia	Very common
	Injection site reaction	Uncommon
	Vasodilation	Very rare
Immune system disorders		
	Anaphylactic response	Uncommon
Hepatobiliary disorders		
	Liver function test abnormal	Common

Description of selected adverse reactions

Infusion hypersensitivity reactions have been associated with abdominal pain, nausea, vomiting, myalgia, pruritus, maculopapular rash, fever, hypotension, shock, bronchospasm, respiratory failure, chest pain and in certain patients a decrease in oxygen saturation and cyanosis.

Renal tubular acidosis has been reported including hyposthenuria and electrolyte imbalance such as increased potassium and decreased magnesium.

Abnormal liver function tests have been reported with ABELCET and other amphotericin B products associated to other factors such as infection, hyperalimentation, concomitant hepatotoxic drugs and graft-versus-host disease.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Paediatric population

Undesirable effects observed in children are similar to those observed in adults.

Other special populations

In a randomised controlled study including patients ≥ 65 years, the adverse reaction profile was similar to that seen in adults less than 65 years. Important exceptions were increases in serum creatinine and dyspnoea which were reported in patients ≥ 65 years for both Abelcet and conventional amphotericin B with a greater frequency in this age group.

4.9 OVERDOSE

Dosages up to 10 mg/kg/day have been administered in clinical studies with no apparent dose-dependent toxicity.

Instances of overdose reported with Abelcet have been consistent with those reported in clinical trials with treatment at standard doses (see section “Adverse Effects”.) In addition, seizures and bradycardia were experienced by one paediatric patient who received a dose of 25 mg/kg.

In case of overdose, the status of the patient (in particular the cardio-pulmonary, renal and hepatic function as well as the blood count and serum electrolytes) should be monitored and supportive measures initiated. No specific antidote to amphotericin B is known.

One paediatric patient received a single dose of 13.1 mg/kg on one occasion, without adverse effects.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Amphotericin B, the active antifungal agent in ABELCET, may be fungistatic or fungicidal, depending on its concentration and on fungal susceptibility. The drug probably acts by binding to ergosterol in the fungal cell membrane causing subsequent membrane damage. As a result, cell contents leak from the fungal cell, and ultimately, cell death occurs. Binding of the drug to sterols in human cell membranes may result in toxicity, although amphotericin B has greater affinity for fungal ergosterols than for the cholesterol of human cells.

Amphotericin B is active against many fungal pathogens *in vitro*, including *Candida sp*., *Cryptococcus neoformans*, *Aspergillus sp*., *Mucor sp*., *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Histoplasma capsulatum*. Most strains are inhibited by amphotericin B concentrations of 0.03 to 1.0 µg/mL.

Amphotericin B has little or no activity against bacteria or viruses. ABELCET shows *in vitro* activity against *Aspergillus sp*. (n=3) and *Candida sp*. (n=10), with MICs generally <1 µg/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 µg/mL). However, standardised techniques for susceptibility testing for antifungal agents have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

Clinical trials

Two randomised comparative studies were conducted in systemic *Candida* and in cryptococcal meningitis. In addition, a comparison was made of open-label treatment of patients with aspergillosis with a retrospectively acquired control group. In the randomised comparative study in patients with invasive candidiasis (153 on 5 mg/kg/day of ABELCET vs 78 on 0.6 to 1.0 mg/kg/day of amphotericin B), the overall response rate was 63% for ABELCET vs 68% for amphotericin B. In the randomised comparative study in patients with cryptococcal meningitis (21 on 5 mg/kg/day of ABELCET vs 17 on 0.7 mg/kg/day of amphotericin B), the overall response rate (clinical and mycological success) was 43% for ABELCET vs 47% for amphotericin B.

A comparison was made of a group of patients with aspergillosis treated with ABELCET with a retrospectively acquired control group of patients treated with amphotericin B. Patients in the ABELCET -treated group were given the product for a variety of reasons which included failure of amphotericin B or another systemic antifungal therapy, nephrotoxicity due to amphotericin B or another drug, renal disease or acute amphotericin B toxicity. There were several differences in the characteristics of the two groups that may have influenced the comparison. Overall clinical response rate (complete and partial response) was 40% for ABELCET vs 20% for amphotericin B.

Information to support efficacy in other fungal infections, including fusariosis, coccidioidomycosis, zygomycosis and blastomycosis, is limited.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Amphotericin B is complexed to phospholipids in ABELCET. The pharmacokinetic properties of ABELCET and conventional amphotericin B are different. Amphotericin B when administered as ABELCET is rapidly distributed to tissues. Limited human autopsy data showed that, after administration of ABELCET, amphotericin B levels in tissue were highest in the liver, spleen and lung. Peak blood levels of amphotericin B were lower after administration of ABELCET than after administration of equivalent amounts of conventional drug.

Available data on the pharmacokinetics of amphotericin B in whole blood after the administration of ABELCET in humans, support an initial rapid fall in the concentration of amphotericin B from the blood followed by a long terminal decline in concentration. However, the physicochemical character of circulating amphotericin B and the pharmacological significance of the level of the drug in blood is not known.

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.

Distribution

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 to 5 mg/kg/day. The pharmacokinetics of amphotericin B in whole blood after the administration of ABELCET and amphotericin B desoxycholate are:

Table 3: 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 ($AUC_{0\text{-}24h}$) (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.

Metabolism

The pharmacokinetics of amphotericin B after the administration of ABELCET are nonlinear.

Excretion

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.

Tissue concentrations of amphotericin B have been obtained at autopsy from one heart transplant patient who received ABELCET at a dose of 5.3 mg/kg/day for three consecutive days immediately before death. The concentrations of amphotericin B (µg/g) reported were: 290, spleen; 222, lung; 196, liver; 7.6, lymph node; 6.9, kidney; 5, heart; 1.6, brain. The relationship of tissue concentrations of amphotericin B to its biological activity when administered as ABELCET is unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Gene mutation assays in Salmonella typhimurium and in mouse lymphoma cells *in vitro* were negative. There was no increase in the incidence of chromosomal aberrations in Chinese hamster ovary cells *in vitro* or in an *in vivo* micronucleus test in mice.

Carcinogenicity

There have been no animal studies conducted to assess the carcinogenic potential of ABELCET.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each mL of ABELCET suspension contains:

Amphotericin equivalent to amphotericin B	5.0 mg
Dimyristoylphosphatidylcholine	3.4 mg
Dimyristoylphosphatidylglycerol (as the sodium and ammonium salts)	1.5 mg
Sodium Chloride	9.0 mg
Water for Injections, sufficient to make	1.0 mL

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Amphotericin equivalent to amphotericin B 100 mg/20 mL; yellow, opaque suspension for infusion; 20 mL vials with filter needles are individually packaged.

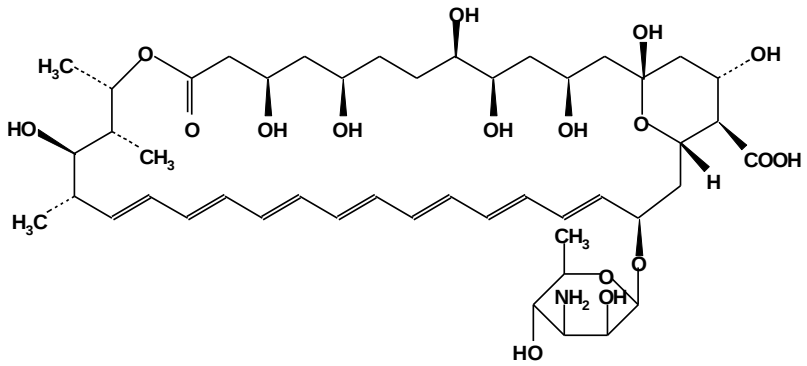
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Unused material should be discarded.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1397-89-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Teva Pharma Australia Pty Limited
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1800 288 382
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9 DATE OF FIRST APPROVAL

20th April 2004

10 DATE OF REVISION

20th June 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Adverse effects information updated, added post-market reports of nephrogenic diabetes insipidus.
4.9	Overdose information added
8	Sponsor information revised