PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Abelcet 5mg/mL Concentrate for Suspension for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amphotericin B Lipid Complex. Each vial contains 5mg Amphotericin B per mL.
Excipients:
Contains 3.6 mg/mL of sodium (0.156 mmol); this represents 71.8 mg of sodium (3.12 mmol) per 20 mL vial.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for suspension for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abelcet is indicated for the treatment of severe invasive candidiasis.

Abelcet is also indicated as second line therapy for the treatment of severe systemic fungal infections in patients who have not responded to conventional amphotericin B or other systemic antifungal agents, in those who have renal impairment or other contra-indications to conventional amphotericin B, or in patients who have developed amphotericin B nephrotoxicity. Abelcet treatment is indicated as second line treatment for invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients, fusariosis, coccidiomycosis, zygomycosis and blastomycosis.

4.2 Posology and method of administration

Abelcet is a sterile, pyrogen-free suspension which must be diluted for intravenous infusion only.

Abelcet should be administered by intravenous infusion at 5 mg/kg at a rate of 2.5 mg/kg/hr.

When commencing treatment with Abelcet for the first time it is recommended to administer a test dose immediately prior to the first infusion. The first infusion should be prepared according to the instructions then, over a period of approximately 15 minutes, 1mg of the infusion should be administered to the patient. After this amount has been administered the infusion should be stopped and the patient observed carefully for 30 minutes. If the patient shows no signs of hypersensitivity the infusion may be continued. As for use with all amphotericin B products, facilities for cardiopulmonary resuscitation should be readily at hand when administering Abelcet for the first time, due to the possible occurrence of anaphylactoid reactions.

For severe systemic infections treatment is generally recommended for at least 14 days.

Abelcet has been administered for as long as 28 months, and cumulative doses have been as high as 73.6 g without significant toxicity.

An in-line filter may be used for intravenous infusion of Abelcet. The mean pore diameter of the filter should be no less than 15 microns.

Use in diabetic patients
Abelcet may be administered to diabetic patients.

Use in paediatric patients
Systemic fungal infections have been treated successfully in children ranging from 1 month to 16 years of age at doses comparable to the recommended adult dose on a bodyweight basis. Adverse events seen in paediatric patients are similar to those seen in adults.

Use in elderly patients
Systemic fungal infections in elderly patients have been treated successfully with Abelcet at doses comparable to the recommended dose on a bodyweight basis.

Use in neutropenic patients
Abelcet has been used successfully to treat systemic fungal infections in patients who are severely neutropenic as a consequence of haematological malignancy or the use of cytotoxic or immunosuppressive drugs.

Use in patients with renal or liver disease
Systemic fungal infections in patients with renal or liver disease have been treated successfully with Abelcet at doses comparable to the recommended dose on a body weight basis (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients , unless in the opinion of the physician the advantages of using Abelcet outweigh the risks of hypersensitivity.

4.4 Special warnings and precautions for use

In patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome), the sodium content of this product should be taken into account (see section 2).

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 be recorded during the first 2 days of administration (see section 4.8).
Premedication (e.g. paracetamol) may be administered for the prevention of infusion related adverse reactions.

Systemic Fungal Infections
Abelcet should not be used for treating common or superficial, clinically inapparent fungal infections that are detectable only by positive skin or serologic tests.

Patients with renal Disease
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 at least once weekly during therapy. Abelcet can be administered to patients during renal dialysis or haemofiltration. Serum potassium and magnesium levels should be monitored regularly.

Patients with liver Disease
Patients with concurrent hepatic impairment due to infection, graft-versus-host disease, other liver disease or administration of hepatotoxic drugs have been successfully treated with Abelcet. In cases where serum bilirubin, alkaline phosphatase or serum transaminases increased, factors other than Abelcet were present and possibly accounted for the abnormalities. These factors included infection, hyperalimentation, concomitant hepatotoxic drugs and graft-versus-host disease.

4.5 Interaction with other medicinal products and other forms of interaction

Nephrotoxic Drugs

Abelcet is a potentially nephrotoxic drug, and particularly close monitoring of renal function is required in patients receiving nephrotoxic drugs concomitantly.

Zidovudine

In dogs, exacerbated myelotoxicity and nephrotoxicity were observed when Abelcet was administered concomitantly with zidovudine. If concomitant treatment with zidovudine is required, renal and haematologic function should be closely monitored.

Cyclosporin

Interaction data with amphotericin B containing products indicate that patients receiving amphotericin B concomitantly with high dose cyclosporine experience an increase in serum creatinine caused by simultaneous administration of these two compounds. However, Abelcet has been shown to be less nephrotoxic than conventional amphotericin B.

Other drugs

The interaction of Abelcet with other drugs has not been studied to date.

Conventional amphotericin B has been reported to interact with the following drugs, and caution should be exercised during concomitant use with Abelcet: antineoplastic agents, corticosteroids and corticotrophin (ACTH), digitalis glycosides, flucytosine, and skeletal muscle relaxants.

Leukocyte transfusions

Acute pulmonary toxicity has been reported in patients receiving intravenous conventional amphotericin B and leukocyte transfusions. It is not recommended to administer Abelcet with leukocyte transfusions

4.6 Pregnancy and lactation

Conventional amphotericin B has been used successfully to treat systemic fungal infections in pregnant women with no obvious effects on the foetus, but only a small number of cases have been reported.

Reproductive toxicity studies of Abelcet in rats and rabbits showed no evidence of embryotoxicity, foetotoxicity or teratogenicity. However, safety for use in pregnant women has not been established for Abelcet. Abelcet should only be administered to pregnant women when the likely benefit exceeds the risk to the mother and foetus.

It is unknown whether Abelcet passes into breast milk. A decision on whether to continue/discontinue nursing or whether to continue/discontinue Abelcet should be made taking into account the benefit of breast-feeding to the child and the benefit of Abelcet to the woman.

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 patients who require Abelcet generally precludes driving or operating machinery

4.8 Undesirable effects

The most common clinical adverse reactions in randomised controlled and open label clinical trials have been chills (16%), increased creatinine (13%), pyrexia (10%), hypokalaemia (9%), nausea (7%) and vomiting (6%).

The incidence is based on analysis from pooled clinical trials of 709 Abelcet treated patients.

There were 556 cases in emergency use studies (open-label, non comparative studies) and 153 in a randomised controlled trial in invasive candidiasis (38% ≥ 65 years). In the emergency use studies, patients had either shown intolerance to conventional amphotericin B treatment, had renal impairment as a result of previous conventional amphotericin B treatment, had pre-existing renal disease or were treatment failures.

The following adverse reactions have been reported with Abelcet during clinical trials and/or post-marketing use.

Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), not known (cannot be estimated from the available data).

System organ class	**Adverse reaction**	**Frequency**
Blood and lymphatic system disorders		
	Thrombocytopenia	Common
Immune system disorders		
	Anaphylactic response	Uncommon
Metabolism and nutrition disorders		
	Hyperbilirubinaemia, Hypokalaemia, Electrolyte imbalance including blood potassium increased, blood magnesium decreased	Common
Nervous system disorders		
	Headache, Tremor	Common
	Convulsion, Neuropathy	Uncommon
	Encephalopathy	Not known
Cardiac disorders		
	Tachycardia, Cardiac Arrhythmias	Common
	Cardiac arrest	Uncommon
Vascular disorders		
	Hypertension, Hypotension	Common
	Shock	Uncommon
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea, Asthma	Common
	Respiratory failure	Uncommon
	Bronchospasm	Not known
Gastrointestinal disorders		
	Nausea, Vomiting, Abdominal pain	Common

System organ class	Adverse reaction	Frequency
Hepatobiliary disorders		
	Liver function tests abnormal	Common
Skin and subcutaneous tissue disorders		
	Rash	Common
	Pruritus	Uncommon
	Dermatitis exfoliative	Not known
Musculoskeletal and connective tissue disorders		
	Myalgia	Uncommon
Renal and urinary disorders		
	Renal impairment including renal failure	Common
	Hyposthenuria, Renal tubular acidosis	Not known
General disorders and administration site conditions		
	Chills, Pyrexia	Very common
	Injection site reaction	Uncommon
Investigations		
	Blood creatinine increased	Very common
	Blood alkaline phosphatase increased, blood urea increased	Common

The undesirable effects listed with frequency “not known” (encephalopathy, bronchospasm, dermatitis exfoliative, hyposthenuria, renal tubular acidosis) have been observed during post-marketing use.
Adverse reactions that have been reported to occur with conventional amphotericin B may occur with Abelcet. In general, the physician should monitor the patient for any type of adverse event associated with conventional amphotericin B.

Infusion hypersensitivity reactions have been associated with abdominal pain, nausea, vomiting, myalgia, pruritus, maculopapular rash, fever, hypotension, shock, bronchospasm, respiratory failure (see section 4.4).

Patients in whom significant renal toxicity was observed following conventional amphotericin B frequently did not experience similar effects when Abelcet was substituted.
Declines in renal function, shown by increased serum creatinine and hypokalaemia, have not typically required discontinuation of treatment.
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.
Although other factors such as infection, hyperalimentation, concomitant hepatotoxic drugs and graft-versus-host disease may be contributory, a causal relationship with Abelcet cannot be excluded. Patients with abnormal liver function tests should be carefully monitored and cessation of treatment considered if liver function deteriorates.

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

In elderly patients, 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 elderly patients for both Abelcet and conventional amphotericin B with a greater frequency in this age group.

4.9 Overdose

Dosages up to 10mg/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 4.8). In addition, seizures and bradycardia were experienced by one paediatric patient who received a dose of 25mg/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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, antibiotics. ATC Code J02A A01

Abelcet consists of the antifungal agent, amphotericin B, complexed to two phospholipids. Amphotericin B 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.

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 ergosterol than for the cholesterol of human cells.

Microbiological activity
Amphotericin B is active against many fungal pathogens in vitro, including Candida spp., Cryptococcus neoformans, Aspergillus spp., Mucor spp., Sporothrix schenckii, Blastomyces dermatitidis, Coccidioides immitis and Histoplasma capsulatum. Most strains are inhibited by amphotericin B concentrations of 0.03-1.0 μg/ml. Amphotericin B has little or no activity against bacteria or viruses. The activity of Abelcet against fungal pathogens in vitro is comparable to that of amphotericin B. However, activity of Abelcet in vitro may not predict activity in the infected host.

5.2 Pharmacokinetic properties

Amphotericin B is complexed to phospholipids in Abelcet. The pharmacokinetic properties of Abelcet and conventional amphotericin B are different. Pharmacokinetic studies in animals showed that, after administration of Abelcet, amphotericin B levels were highest in the liver, spleen and lung. Amphotericin B in Abelcet was rapidly distributed to tissues. The ratio of drug concentrations in tissues to those in blood increased disproportionately with increasing dose, suggesting that elimination of the drug from the tissues was delayed. Peak blood levels of amphotericin B were lower after administration of Abelcet than after administration of equivalent amounts of conventional drug. Administration of conventional amphotericin B resulted in much lower tissue levels than did dosing with Abelcet. However, in dogs, conventional amphotericin B produced 20-fold higher kidney concentrations than did Abelcet given at comparable doses.

The pharmacokinetics of Abelcet in whole blood were determined in patients with mucocutaneous leishmaniasis. Results for mean pharmacokinetic parameters at 5.0 mg/kg/day were as follows:

	Abelcet
Dose: (mg/kg/day)	5.0
Peak blood level C_{max}: (μg/ml)	1.7
Area under time-concentration curve AUC $_{0-24}$: (μg.hr/ml)	9.5
Clearance: (ml/hr.kg)	211.0
Volume of distribution Vd: (l/kg)	2286.0
Half-life T½: (hr)	173.4

The rapid clearance and large volume of distribution of Abelcet result in a relatively low AUC and are consistent with preclinical data showing high tissue concentrations. The kinetics of Abelcet are linear, the AUC increases proportionately with dose.

Details of the tissue distribution and metabolism of Abelcet in humans, and the mechanisms responsible for reduced toxicity, are not well understood. The following data are available from necropsy in a heart transplant patient who received Abelcet at a dose of 5.3 mg/kg for 3 consecutive days immediately before death:

Organ	Abelcet tissue concentration expressed as amphotericin B content (mg/kg)
Spleen	290.0
Lung	222.0
Liver	196.0
Kidney	6.9
Lymph node	7.6
Heart	5.0
Brain	1.6

5.3 Preclinical safety data

Acute toxicity studies in rodents showed that Abelcet was 10-fold to 20-fold less toxic than conventional amphotericin B. Multiple-dose toxicity studies in dogs lasting 2-4 weeks showed that on a mg/kg basis, Abelcet was 8-fold to 10-fold less nephrotoxic than conventional amphotericin B. This decreased nephrotoxicity was presumably a result of lower drug concentrations in the kidney.

Since conventional amphotericin B first became available, there have been no reports of drug-related carcinogenicity, mutagenicity, teratogenicity or adverse effect on fertility. Abelcet has been shown not to be mutagenic by the in vivo mouse micronucleus assay, in vitro bacterial and lymphoma mutation assays, and an in vivo cytogenetic assay. It has been shown not to be teratogenic in mice and rabbits.

Phospholipids are essential constituents of human cell membranes. The average diet provides several grams of phospholipids each day. There is no evidence that phospholipids, including DMPC and DMPG, are carcinogenic, mutagenic or teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-α-dimyristoylphosphatidylcholine (DMPC)
L-α-dimyristoylphosphatidylglycerol (sodium and ammonium salts) (DMPG)
Sodium Chloride
Water for Injection

6.2 Incompatibilities

Abelcet should not be mixed with other drugs or electrolytes.

6.3 Special precautions for storage

Store at 2 - 8°C. Do not freeze. Keep vial in the outer carton

6.4 Nature and contents of container

Abelcet is a sterile, pyrogen-free yellow suspension in a type I glass single use vial containing 20 ml (100 mg amphotericin B). The vial is sealed with a rubber stopper and aluminum seal. Vials are packaged in cartons of 10 vials.

6.5 Special precautions for disposal and other handling

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

Preparation of the suspension for infusion

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF Abelcet, SINCE NO BACTERIOSTATIC AGENT OR PRESERVATIVE IS PRESENT.

Allow the suspension to come to room temperature. Shake gently until there is no evidence of any yellow settlement at the bottom of the vial. Withdraw the appropriate dose of Abelcet from the required number of vials into one or more sterile 20 ml syringes using a 17 to 19 gauge needle. Remove the needle from each syringe filled with Abelcet and replace with the 5 micron high flow filter needle (supplied by B. Braun Medical, Inc.) provided with each vial. Insert the filter needle of the syringe into an IV bag containing 5.0% Dextrose for Injection and empty the contents of the syringe into the bag using either manual pressure or an infusion pump. The final infusion concentration should be 1 mg/ml. For paediatric patients and patients with cardiovascular disease the drug may be diluted with 5.0% Dextrose for Injection to a final infusion concentration of 2 mg/ml. Do not use the agent after dilution with 5.0% Dextrose for Injection if there is any evidence of foreign matter. Vials are single use. Unused material should be discarded. 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% Dextrose for Injection before infusion of Abelcet or a separate infusion line should be used.

The diluted ready for use suspension may be stored at 2°C - 8°C for up to 24 hours prior to use. Shake vigorously before use. Do not store for later use.

7 REGISTRATION NUMBER

153 06 34069 00.

8 MANUFACTURER

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