Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Abelcet 5mg/ml Concentrate for Suspension for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amphotericin B Liquid Complex. Each ml contains 5mg Amphotericin B.

Each vial contains 20ml (100mg, 100,000IU of amphotericin B) which must be diluted before intravenous infusion.

Abelcet contains 3.6 mg/ml of sodium (0.156 mmol); this represents 71.8 mg of sodium (3.12 mmol) per 20ml vial.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for suspension for Infusion
Abelcet is a sterile, pyrogen free yellow suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

First-line treatment of aspergillosis

Abelcet is indicated for the first-line treatment of aspergillosis in immunocompromised and immunocompetent patients.

First-line treatment of systemic candidal infections

Abelcet is indicated for first-line treatment of systemic candidal infections in neutropenic and non-neutropenic patients. In a randomised, comparative study against conventional amphotericin B, the two treatments were equally efficacious in terms of clinical improvement and in the eradication of fungal pathogens. However, a comparison of patients' renal function showed that Abelcet was significantly better tolerated than conventional amphotericin B.
A statistically significant delay in deterioration of renal function was observed in the Abelcet patients compared to those treated with conventional amphotericin B.

First line treatment of cryptococcal meningitis

Abelcet is also indicated for first line treatment of cryptococcal meningitis and systemic cryptococcosis in patients with acquired immunodeficiency syndrome (AIDS). In a comparative clinical study in AIDS patients with cryptococcal meningitis, the efficacy of Abelcet was comparable to that of conventional amphotericin B. However, the toxicity, particularly the nephrotoxicity, of Abelcet was markedly less, allowing administration of considerably higher doses for a prolonged period.

Severe systemic fungal infections

Abelcet is indicated 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 contraindications to conventional amphotericin B, or in patients who have developed amphotericin B nephrotoxicity. In an open-label emergency use study of Abelcet in these patient groups, 74/111 (67 %) patients experienced clinical cure or improvement, and in 37/67 (55 %) where fungal pathogens were isolated, mycological eradication was achieved.

Fungal infections that have responded to Abelcet treatment include systemic candidiasis, aspergillosis, cryptococcal meningitis and disseminated cryptococcosis, fusariosis, zygomycosis, blastomycosis and coccidioidomycosis. Abelcet may also be effective in the treatment of histoplasmosis, chronic mycetoma, pseudallescheriasis, sporotrichosis and trichosporosis.

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

4.2 Posology and method of administration

Abelcet is a sterile, pyrogen-free suspension to be diluted for intravenous infusion only. The recommended daily dose is 5.0 mg/kg given as a single infusion.

Abelcet should be administered by intravenous infusion 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 15 minutes approx. 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 resuscitation should be readily at hand when administered Abelcet® for the first time, due to the possible occurrence of anaphylactoid reactions. Data are presently insufficient to define the total dose and treatment duration necessary for successful treatment. However, for severe systemic infections treatment duration should be 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.

An in-line filter may be used for intravenous infusion of Abelcet. The mean pore diameter of the filter should not be less than 15.0 microns.

Use in diabetic patients

Abelcet can be administered to diabetic patients at doses comparable to the recommended dose on a bodyweight basis.

Paediatric use

Systemic fungal infections in children (ranging from 1 month to 16 years of age) have been treated successfully with Abelcet at doses comparable to the recommended adult dose on a body weight basis.

Use in elderly patients

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

Use in patients with serious concomitant illnesses, renal impairment or hepatic insufficiency

The recommended dose is 5.0 mg/kg/day in these patients**.** See section 4.4 Special warnings and precautions for use.

Use in renal dialysis patients and in patients with renal failure

Abelcet should be administered to renal dialysis patients only after the completion of dialysis. Abelcet may be given to patients with renal failure at the recommended adult dose.

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

Adverse reactions may occur, and are likely to be similar to those associated with conventional amphotericin B. To detect idiosyncratic anaphylactic reactions and to minimise the dose administered if such a reaction occurs, a test dose should be administered initially. Particular attention should be paid to patients receiving nephrotoxic drugs concomitantly with Abelcet. Renal function should be closely monitored in these patients.

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.

Serum potassium and magnesium levels should be monitored regularly.

Analysis of renal function test results has shown that during Abelcet treatment renal function remains stable or improves, rather than declines. In patients with serious systemic fungal infections and contraindications to conventional amphotericin B, the mean serum creatinine decreased from 174.4 µmol/l at baseline to 130.0 µmol/l after 6 weeks of treatment. In the subpopulation of cases with baseline serum creatinine levels of 221.0 µmol/l or greater, the mean serum creatinine decreased from 341.2 µmol/l at the start of treatment to 192.7 µmol/l after 6 weeks of treatment. Renal dysfunction that developed during treatment with conventional amphotericin B has been shown to stabilize or improve during subsequent Abelcet treatment.

As with all treatments in this case, hepatic impairment may occur. Hepatic monitoring is recommended. However, 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.

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

Infusion Hypersensitivity Reactions
Premedication may be considered for the prevention of infusion related reactions (see section 4.8). Paracetamol, diphenydramine, pethidine, and/or hydrocortisone have been reported as successful in the prevention and treatment of such reactions.

Systemic fungal infections
Abelcet should not be used for treatment of common or superficial, clinically unapparent fungal infections that are detectable only by positive skin or serologic tests.

4.5 Interaction with other medicinal products and other forms of interaction

The interaction of Abelcet with other drugs has not been studied to date. Patients requiring concomitant medications should be closely observed. Specifically, in patients receiving nephrotoxic drugs, renal function should be closely monitored. Conventional amphotericin B has been reported to interact with antineoplastic agents, corticosteroids and corticotropin (ACTH), digitalis glycosides. flucytosine and skeletal muscle relaxants.

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.

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. This possible interaction has not been investigated in humans. If concomitant treatment with both agents is required, renal and haematologic function should be closely monitored.

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.

4.6 Fertility, 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. Therefore, Abelcet should be administered to pregnant women only for life-threatening disease 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 in Section 4.8 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, increased creatinine, pyrexia, hypokalaemia, nausea and vomiting at levels of 16, 13, 10, 9,7 and 6% respectively.

The following undesirable effects have been reported with Abelcet during clinical trials and/or post-marketing use. The incidence is based on analysis from pooled clinical trials of 709 Abelcet treated patients (556 from emergency use studies and 153 from a randomised controlled trial in candidiasis).

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) and not known (can not be estimated from the available data).

System Organ class	Adverse reaction	Frequency
Infections and infestations		
	Infection, Sepsis	Uncommon
Blood and lymphatic system disorders		
	Anaemia, Leukopenia, Thrombocytopenia	Common
	Coagulopathy, Eosinophilia, Haemolytic anaemia, Leukaemoid reaction, Pancytopenia	Uncommon
Immune system disorders		
	Anaphylactoid reaction, Hypersensitivity, Transplant rejection	Uncommon
Metabolism and nutrition disorders		
	Acidosis, Hyperbilirubinaemia, Hypokalaemia, Hypomagnesaemia, Electrolyte imbalance including hyperkalaemia, disturbance of serum calcium, chloride, phosphate.	Common
	Alkalosis, Anorexia, Hyperlipidaemia, Hypernatraemia, Hyperuricaemia	Uncommon
Psychiatric disorders		
	Anxiety, Nervousness	Uncommon
Nervous system disorders		
	Headache, Tremor	Common
	Agitation, Choreoathetosis, Confusional state,	Uncommon

	Convulsion, Dizziness, Hypertonia, Hypoaesthesia, Neuropathy, Nuchal rigidity, Paraesthesia, Peroneal nerve palsy, Somnolence, Speech disorder, Stupor, Thinking abnormal	
Ear and labyrinth disorders		
	Deafness, Tinnitus	Uncommon
Cardiac disorders		
	Tachycardia, Arrythmias including Supraventricular tachycardia, Bradycardia, Atrial fibrillation, Atrioventricular block second degree and Ventricular extrasystoles	Common
	Cardiac failure, Cyanosis, Palpitations, Cardiac arrest	Uncommon
Vascular disorders		
	Hypertension, Hypotension	Common
	Angiopathy, Pallor, Phlebitis, Pulmonary embolism, Shock, Vasodilatation, Venoocclusive liver disease	Uncommon
Respiratory, thoracic and mediastinal disorders		
	Asthma, Dyspnoea, Hyperventilation, Respiratory disorder	Common
	Cough, Hypoxia, Pulmonary oedema, Respiratory failure, Rhinitis	Uncommon
	Bronchospasm	Not known
Gastrointestinal disorders		
	Diarrhoea, Nausea, Vomiting, Abdominal pain	Common
	Abnormal faeces, Constipation, Dry mouth, Dysgeusia, Dyspepsia, Dysphagia, Flatulence, Gastrointestinal haemorrhage including rectal and gingival, Pancreatitis, Stomatitis, Tongue discolouration	Uncommon
Hepatobiliary disorders		
	Liver function tests abnormal	Common
	Cholelithiasis, Hepatitis, Hepatocellular damage, Hepatorenal syndrome, Jaundice	Uncommon
Skin and subcutaneous tissue disorders		
	Rash	Common
	Ecchymosis, Hyperhidrosis, Petechiae, Pruritus, Rash maculo-papular, Skin discolouration, Skin ulcer, Urticaria	Uncommon
	Dermatitis exfoliative	Not known
Musculoskeletal, connective tissue and bone disorders		
	Arthalgia, Bone pain, Muscle spasms, Myalgia	Uncommon
Renal and urinary disorders		
	Renal impairment including renal failure	Common
	Anuria, Haematuria, Nephropathy toxic, Oliguria, Urine abnormality	Uncommon
	Hyposthenuria, Renal tubular acidosis	Not known
General disorders and administration site conditions		
	Chills, Pyrexia	Very common
	Asthenia, Generalised oedema	Common
	Back pain, Chest pain, Injection site hypersensitivity, Malaise, Multi-organ failure, Injection site reaction	Uncommon
Investigations		

	Blood creatinine increased	Very common
	Blood alkaline phosphatase increased, Blood urea increased	Common
	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood lactate dehydrogenase increased, Creatinine renal clearance decreased, Electrocardiogram abnormal, Pulmonary function test decreased, Weight increased	Uncommon

A further 178 patients from clinical trials involving non-homogenous patient populations yielded an adverse reaction profile similar to that described above.

Infusion related reactions (such as chills and pyrexia) recorded following the administration of Abelcet have generally been moderate, and have mainly been recorded during the first 2 days of administration. These reactions may be relieved using appropriate pre-medication, see Section 4.4 Special Warnings and Precautions for Use.

Infusion hypersensitivity reactions have been associated with abdominal pain, nauseas, vomiting, myalgia, pruritus, maculopular rash, fever, hypotension, shock, bronchospasm, respiratory failure.

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

The majority of adverse reactions seen commonly with Abelcet (i.e. in the "very common" and "common" frequency categories) have also been observed with other drug products in this class.

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. In randomised, controlled, comparative studies against conventional amphotericin B, patients with hepatic dysfunction at entry to the studies had relatively less deterioration in hepatic impairment in the Abelcet arms compared to patients treated with conventional amphotericin B.

Data from a randomised, controlled, comparative study demonstrated that renal function remained stable in the majority of patients who had normal renal function and who had not previously been treated with conventional amphotericin B.

Renal dysfunction that developed during treatment with conventional amphotericin B has been shown to stabilize or improve during subsequent Abelcet treatment. Diminished renal function resulted in the withdrawal of 15% of patients treated with conventional amphotericin B as compared to 6% of patients treated with Abelcet in randomised comparative studies. An increase in serum creatinine resulted in drug discontinuation more than four times as frequently in the conventional amphotericin B patients (10%) then in the Abelcet treated patients (2%).

In an open label study including paediatric patients, the adverse reaction profile reported was similar to that in adults with chills and pyrexia being the most commonly observed reactions.

In a randomised controlled study including patients ≥65 years, the adverse reaction profile was similar to that seen in younger adults, with the important exceptions that increases in serum creatinine and dyspnoea were reported 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

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.

ATC Code
J02A A01

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., C*ryptococcus 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 g/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 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}: (g/ml)	1.7
Area under time-concentration curve AUC_{0-24}: (g•hr/ml)	9.5
Clearance: (ml/hr/kg)	211.0
Volume of distribution Vd: (l)	2286.0
Half-life $T_{½}$: (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 and 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Abelcet should not be diluted in sodium chloride solution, or mixed with other drugs or electrolytes. It is incompatible with Saline Solution.

6.3 Shelf life

Unopened: 2 years

Chemical and physical in-use stability of prepared intravenous solutions in 5% Dextrose Injection has been demonstrated for 48 hours at 2° to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° C – 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

Preparation of the suspension for infusion
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 syringes. Remove the needle from each syringe filled with Abelcet and replace with the 5 micron filter high flow 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 content of the syringe into the bag. Each filter needle must only be used to filter the contents of one vial, and a new filter needle should be used for each subsequent vial. 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.

Aseptic technique must be strictly observed throughout handling of Abelcet, since no bacteriostatic agent or preservative is present. 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.

Single use vial. Discard unused contents. Do not store for later use.

7 MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
Ridings Point
Whistler Drive
Castleford
West Yorkshire WF10 5HX
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0827/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 May 1996

Date of last renewal: 01 May 2006

10 DATE OF REVISION OF THE TEXT

April 2012