APPENDIX 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ABELCET 5 mg/ml, Concentrate for Suspension for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 20 ml vial contains
amphotericin B ……100.00 mg

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

Treatment of systemic aspergillosis and candidiasis:
• in patients who have developed nephropathy on amphotericin B, defined by:
- the elevation of serum creatinine levels to above 220 micromol/l
or
- the reduction of creatinine clearance to below 25 ml/min.

• in cases of persistent pre-existing impaired renal function, defined by:
- serum creatinine levels above 220 micromol/l
or
- creatinine clearance below 25 ml/min.

4.2. Posology and method of administration

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

The recommended dose is 5 mg/kg/day for 14 to 21 day. Abelcet should be administered by intravenous infusion at a rate of 2.5 mg/kg/hour.

When commencing treatment with Abelcet for the first time it is recommended to administer for 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 resuscication 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 atleast 14 days.

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

An in-line filter maybe 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 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 a successfully with Abelcet at doses comparable to the recommended dose on a bodyweight basis.

In the event of renal function deteriorating on Abelcet, a risk/benefit assessment should be made before deciding whether to continue treatment. In the absence of a valid dose-adaptation schedule, it is recommended that the dose of Abelcet is temporarily reduced to 2.5 mg/kg or the infusions given at longer intervals.

With the current state of knowledge, however, there is no schedule that guarantees both the efficacy and the safety of the treatment.

4.3. Contraindications

Abelcet is contraindicated in patients with hypersensitivity to any of the components of the medicinal product.

4.4. Special warnings and precautions for use

This is a prescription only medicine for hospital use.

Infusion hypersensitivity reactions
The initial doses are to be administered under medical supervision, until treatment has been stabilised, in order to confirm that the patient shows no immediate hypersensitivity and to determine the optimal dose (see section 4.2 Posology and method of administration).
Acute reactions such as chills, fever, anorexia, nausea, vomiting, headache, myalgia, arthralgia and hypotension are common when amphotericin B is given intravenously. These symptoms may be reduced by the administration of antihistamines, antiemetics, antipyretics or corticosteroids.

Systemic funfal infections
Abelcet should not be used for treating common or superficial, clinically inapparent infections that are detectable only be 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 failure, and at least once weekly during therapy.

Patients using sultopride
This medicinal product is generally not recommended with sultopride (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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 phosphatise 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.

Renal function (see section 4.8 Undesirable effects), the electrolyte balance (in particular, potassium and magnesium), hepatic function, and the full blood count should be monitored regularly during treatment.

4.5. Interaction with other medicinal products and other forms of interaction

+ Medicines that induce hypokalaemia
Hypokalaemia is a factor that potentiates cardiac arrhythmias, in particular torsades de pointes) and potentiates the toxicity of certain medicines, such as digoxin. Given this fact, medicines that may induce hypokalaemia are involved in a large number of interactions. They include potassium-lowering diuretics, alone or in combination, stimulant laxatives, glucocorticoids, tetracosactide and amphotericin B (by the intravenous route).

+ Nephrotoxic medicines
The concomitant use of medicines with a toxic effect on the kidneys increases the risk of nephrotoxicity. If such a combination is necessary, renal function must be monitored more closely.
The medicines mainly concerned are iodine-containing contrast media, aminosides, organoplatinum compounds, high doses of methotrexate, certain antiviral agents such as pentamidine, foscarnet, the '-ciclovirs', ciclosporin and tacrolimus.

<u>Concomitant medication not recommended (see section 4.4. Special warnings and precautions for use):</u>
+ Sultopride
Serious risk of ventricular arrhythmias, particularly torsades de pointes.

<u>Caution should be exercised with the concomitant use of:</u>
+ Other potassium-lowering medicines
Potassium-lowering diuretics (alone or in combination), stimulant laxatives, gluco- and mineralocorticoids (systemic administration), and tetracosactide.
Serious risk of hypokalaemia.
Monitor potassium levels and correct if necessary, especially in patients on concomitant treatment with cardiac glycosides.

+ Cardiac glycosides (digitalis)
Hypokalaemia potentiates the toxic effects of cardiac glycosides.
Correct any hypokalaemia beforehand and monitor the patient clinically, keeping a close eye on the electrolyte balance and ECG.

+ Medicines likely to trigger torsades de pointe (other than sultopride):

Class Ia antiarrhythmic agents (quinidine, hydroquinidine, disopyramide) and class III antiarrhythmic agents (amiodarone, sotalol, dofetilide, ibutilide), certain neuroleptics (thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, amisulpride, tiapride, sulpiride, haloperidol, droperidol, pimozide), bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, lumefantrine methadone, mizolastine, moxifloxacin, pentamidine, spiramycin IV, veralipride, vincamine IV, etc.
Serious risk of ventricular arrhythmia, especially torsades de pointes.
Correct any hypokalaemia before administering this medicinal product and monitor the patients clinically, checking the electrolytes and ECG.

+ Zidovudine
Increases haematological toxicity (cumulative toxic medullary effects).
Do a full blood count more often.

Other possible interactions
+ Aminosides
Cumulative risk of nephrotoxicity

+ Ciclosporin, tacrolimus
Greater increase in creatinine levels than on the immunosuppressants alone (synergistic nephrotoxic effects of the two substances).

4.6. Pregnancy and lactation

Pregnancy Category B
Reproduction studies have been performed in animals and have revealed no evidence of harm to the fetus due to Abelcet. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

It is unknown whether Abelcet is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or whether to continue/discontinue therapy with Abelcet should be made taking into account the benefit of breast-feeding to the child and the benefit of Abelcet therapy 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 the 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 previous conventional amphotericin B treatment, had pre-existing renal disease or were treatment failures.

Premedication (e.g. with paracetamol) may be given to prevent infusion-related adverse reactions. The main undesirable effects include chills, fever, nausea and vomiting.

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 to <1/10), uncommon (≥1/1000 to <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
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

Infusion hypersensitivity reactions have been associated with abdominal pain, nausea, vomiting, myalgia, pruritis, 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 renal 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 casual 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.

To report any side effect(s):

- **Saudi Arabia:**

The National Pharmacovigilance and Drug Safety Centre (NPC)
- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2340.
- Toll free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

- **Other GCC States:**

- Please contact the relevant competent authority.

4.9. Overdose

In the event of overdose, impaired renal function and electrolyte imbalance are the most likely effects. In this case, stop the infusion and initiate symptomatic treatment.

An overdose of amphotericin B may cause cardiovascular arrest in children.

No specific antidote to amphotericin B is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ANTIMYCOTIC FOR SYSTEMIC USE

ATC code J02AA01

(J: general anti-infective agent for systemic use)

Abelcet consists of the antifungal agent, amphotericin B, complexed to two phospholipids. Amphotericin B is a macrocyclic, polyene, broad-spectrum antibiotic produced by *Streptomyces nodosus.* The lipophilic moiety of amphotericin B allows molecules of the drug to be complexed with the phospholipids in a ribbon-like structure.

Mechanism of action

Amphotericin B, the active antifungal agent in Abelcet, may be fungistatic or fungicidal, depending on its concentration and the fungal sensitivity. The medicinal product probably acts by binding to ergosterol in the fungal cell membrane, causing damage to the membrane. As a result, the cell contents leak out of the fungal cell, leading to cell death.

Binding of the amphotericin B to sterols in human cell membranes may result in toxicity, even though amphotericin B has a greater affinity for fungal ergosterol than for the cholesterol in human cells.

Microbiological activity

Amphotericin B is active against the following systemic fungal pathogens: *Candida albicans, Rhodotorula, Aspergillus fumigatus, Cryptococcus neoformans, Mucor mucedo, Absidia, Rhizopus, Histoplasma capsulatum, Blastomyces dermatitidis, Sporathrix schenckii* in disseminated sporotrichosis, and *Coccidioides immitis.*

Amphotericin B has a weak or variable action against the pathogens responsible for the following systemic mycoses:

Candida non albicans, especially *C. parapsilosis, Aspergillus fumigatus* in aspergilloma, *Conidiobolus, Sporathrix schenckii* in lymphocutaneous sporotrichosis, *Coccidioides immitis* in diffuse pulmonary disease.

The activity of Abelcet on pathogenic fungal species in vitro is comparable with that of amphotericin B.

Nevertheless, the in vitro activity of Abelcet does not predict its efficacy in infected host cells.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters obtained with the recommended dose of 5 mg/kg given intravenously over one to two hours are as follows:

- Peak blood level, C_{max}: 2.0 ± 0.8 mg/l (0.9-3.8 mg/l) (about 30-50% weaker than the C_{max} obtained with conventional amphotericin B)
- Half-life, $T_{1/2}$: 173.4 ± 78 hours (68-303 hours) (comparable to that of conventional amphotericin B).
- Volume of distribution (Vd): 43 ± 5 l/kg (37-50 l/kg).
- Total clearance: 3.5 ± 2.1 ml/min/kg (1.9-8.2 ml/min/kg)

The kinetics are linear at doses of 0.10-5 mg/kg.

No notable accumulation was seen with repeated administration up to 42 hours.

The amphotericin B in Abelcet is rapidly distributed throughout the tissues. The ratio between the tissue concentrations and blood levels increases disproportionately with higher doses, which can be interpreted as preferential binding of the medicinal product in the tissues (the volume of distribution with Abelcet is four to ten times greater than that of conventional amphotericinB).

Tissue levels after the administration of conventional amphotericin B are lower than those seen with Abelcet. On the other hand, in the dog, equivalent doses of Abelcet gave concentrations in the kidney that were 20 times lower than those obtained with conventional amphotericin B.

Details of the tissue distribution and metabolism of Abelcet in humans, and the mechanisms responsible for the reduced toxicity in humans, are not well understood.

The following data were obtained postmortem from a heart transplant patient who had been given Abelcet at a dose of 5.3 mg/kg/day for three consecutive days before he died. The tissue concentrations of Abelcet, expressed as amphotericin B (mg/kg), were: spleen 290.0, lungs 222.0, liver 196.0, kidney 6.9, lymph node 7.6, heart 5.0, and brain 1.6.

Urinary excretion is a minor route of elimination.

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, mutagenecity, teratogenecity or adverse effects 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. Excipients

L-α-dimyristoylphosphatidylcholine (DMPC), L-α-dimyristoylphosphatidylglycerol (DMPG) (sodium and ammonium salts), sodium chloride, water for injection

6.2. Incompatibilities

Abelcet suspension must be diluted in a pure 5% dextrose solution. Do not dilute with saline solutions or mix with other drugs or electrolytes.

6.3. Shelf life

Two years

6.4. Special precautions for storage

Store between +2°C and +8°C (in the refrigerator) and protect from light. Keep vial in the outer carton. Do not freeze.

6.5. Nature and contents of container

Abelcet is a sterile, pyrogen-free yellow suspension in a type 1 glass single use vial containing 10 ml or 20 ml (50 mg or 100 mg amphotericin B). The vial is sealed with a rubber stopper and aluminium seal. Vials are packaged in cartons of 1 vial and 10 vials. Not all pack sizes may be marketed.

6.6. Instructions for use and handling

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

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 ml vials. Insert the filter needle of the syringe into an IV bag containing 5% Dextrose Injection and empty the contents of the syringe into the bag. The final infusion concentration should be 1 mg/ml. For pediatric patients and patients with cardiovascular disease the drug may be diluted with 5% Dextrose Injection to a final infusion concentration of 2 mg/ml. Before infusion, shake the bag until the contents are thoroughly mixed. Do not use the admixture after dilution with 5% Dextrose Injection if there is any evidence of foreign matter. Vials are for single use. Unused material should be discarded. Aseptic technique must be strictly observed throughout handling of Abelcet, since no bacteriostatic 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 up to 48 hours at 2^{o} to 8^{o} C and an additional 6 hours at room temperature.

7. MARKETING AUTHORISATION HOLDER

ACINO FRANCE SAS
76-78, AVENUE DU MIDI
63800 COURNON D`AUVERGNE
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

(To be completed)

9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION

(To be completed)

10 DATE OF LAST REVISION

31.07.2014

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARING RADIOPHARMACEUTICALS

Not applicable

13. LEGAL CATEGORY/PHARMACY STATUS

List I
Prescription only medicine for hospital use