

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABELCET® 5mg/ml Concentrate for Suspension for Infusion

Amphotericin B Lipid Complex

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What ABELCET is and what it is used for
2. Before you use ABELCET
3. How to use ABELCET
4. Possible side effects
5. How to store ABELCET
6. Further information

1. WHAT ABELCET IS AND WHAT IT IS USED FOR

ABELCET is a medicine to treat severe fungal infections such as blood infection with candida, aspergillus, cryptococcus, fusarium, zygomycetes, blastomycetes or coccidioides, or cryptococcal meningitis (inflammation of the brain). Fungi are common and are found throughout nature but do not normally cause infections. However, under certain circumstances, for instance, when the body's immune system is not working properly, a few types of fungi can infect humans.

2. BEFORE YOU USE ABELCET

Do not use ABELCET

If you are allergic (hypersensitive) to amphotericin B or any of the other ingredients of ABELCET. For a full list of ingredients please refer to section 6 (What ABELCET contains).

Take special care with ABELCET

- Your doctor may need to monitor you carefully and do some extra tests while you are being treated with ABELCET, particularly if you have had previous problems with your kidneys or liver.
- If you have a kidney problem, your doctor will perform a blood test at least once a week to check how your kidneys are working while you are receiving ABELCET.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

ABELCET may interact with

- drugs which can affect your kidney function
- other drugs such as zidovudine (used to treat HIV infection) or ciclosporin (a drug to suppress your immune system).

Amphotericin B has been reported to interact with the following drugs:

- drugs to treat cancer
- corticosteroids and corticotrophin (ACTH) (drugs given to treat a variety of conditions such as allergies and hormone imbalances)
- digitalis glycosides (used to treat heart conditions)

- flucytosine (used to treat fungal infections)
- muscle relaxants.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

Inform your doctor if you are pregnant or breast feeding. S/He will decide if this medication is suitable for you.

Driving and using machines

You should avoid driving a vehicle or operating machinery after treatment with ABELCET as the side effects of ABELCET could affect your ability to drive safely.

Important information about some of the ingredients of ABELCET

This medicinal product contains 0.156 mmol (or 3.6 mg) sodium per mL. This represents 3.12 mmol (or 71.8 mg) sodium per 20 mL vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE ABELCET

Method and route of administration

ABELCET must be diluted with a dextrose (sugar) solution before use.

ABELCET must be administered as an infusion to the vein. This will be given by a drip into a vein in your arm over about 2 hours.

Dosage and frequency of administration

ABELCET will normally be given to you by your doctor or by a nurse.

The recommended daily dose is 5.0 mg of ABELCET for every kg of your body weight, given as a single infusion. A test dose of 1 mg is given initially to see if you are sensitive to any of the ingredients. The number of days over which you will be treated depends on many factors, but will probably be at least 14 days.

No change in dose is required for children, elderly people and those suffering from kidney or liver disease.

Before you stop using ABELCET

It is important that you follow your doctor's instructions and receive all the medication prescribed for you even if you feel better.

If too much ABELCET is given

You should tell your doctor immediately if you think you received too much ABELCET.

You may experience side effects as listed in section 4 "Possible side effects". Your doctor may need to check your heart and breathing rates, your kidney and liver function, your blood cell counts or the level of potassium in your body.

If a dose is missed

You should tell your doctor immediately, he will decide when you should be given your next dose of ABELCET.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ABELCET can cause side effects, although not everybody gets them.

Uncommon allergic reactions (affecting 1 to 10 people in 1000)

Seek medical help immediately if you have any of the following symptoms of a serious allergic reaction:

- Difficulty breathing and/or feeling dizzy or faint
- Severe itching of the skin or raised lumps on the skin
- Swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing

You should also seek urgent medical help if you have any of the following serious side effects:

- Severe chest pain (heart attack) or difficulty breathing
- Encephalopathy (a disease of the brain, which may cause you to become confused or behave strangely, and/or feel drowsy)

You may experience chills, fever, nausea (feeling sick), vomiting (being sick), rash, itching, muscle pain, abdominal pain or convulsions (fits) although this will probably only occur during the infusion or in the first 2 days of treatment. Your nurse or doctor may be able to arrange some simple treatment to help control these side effects.

ABELCET may affect your kidney, liver or blood. Your doctor will check for these and other unwanted effects by carrying out appropriate tests, for example checking the level of potassium in your body.

Very common side effects (occurring in more than 1 in 10 people)

Chills, fever, increased levels of a substance called creatinine in the blood

Common side effects (affecting 1 to 10 people in 100)

Increased heart rate, irregular heartbeat, low or high blood pressure, low blood platelets (which can lead to an increased risk of bleeding), breathing problems, asthma, nausea (feeling sick), vomiting (being sick), headache, shaking, kidney problems (signs include tiredness and passing less urine), kidney function tests abnormal, increased or decreased blood potassium levels (which can make you feel tired, confused, and have muscle weakness or cramps or make your heart beat abnormally), decreased blood magnesium levels (which can give you "pins and needles", muscular pains, weakness or spasms), liver function tests abnormal, rash

Uncommon side effects (affecting 1 to 10 people in 1000)

Injection site reactions, convulsions (fits), neuropathy (nerve disease)

The following side effects have also been reported with the use of ABELCET but it is not known how often they occur: Widespread flaking or scaling of the skin, the production of large amounts of weak (watery) urine

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE ABELCET

Keep out of the reach and sight of children.

Do not use ABELCET after the expiry date which is stated on the label.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep vial in the outer carton.

6. FURTHER INFORMATION

What ABELCET contains

- The active substance is Amphotericin B.

- The other ingredients are L- α -dimyristoylphosphatidylcholine (DMPC), L- α -dimyristoylphosphatidylglycerol (sodium and ammonium salts) (DMPG), sodium chloride (common salt) and water for injection.

What ABELCET looks like and contents of the pack

ABELCET is supplied as a yellow concentrate for suspension for infusion.

Each vial contains 5 mg Amphotericin B per ml. Vials of 10 ml contain 50 mg amphotericin B. Vials of 20 ml contain 100 mg amphotericin B. Vials are packaged in cartons of 10 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder

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The following information is intended for medical or healthcare professionals only:

Health Care Professional Leaflet

ABELCET® 5mg/ml Concentrate for Suspension for Infusion

Amphotericin B Lipid Complex

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: 3.6 mg/mL of sodium (0.156 mmol); this represents 71.8 mg of sodium (3.12 mmol) per 20 mL vial.

3. CLINICAL PARTICULARS

3.1 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.

3.2 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 3.4).

3.3 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.

3.4 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.

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 3.8).

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.

3.5 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.

3.6 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.

3.7 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.

3.8 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 and 153 in a randomised controlled trial in invasive candidiasis (38% \geq 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 ($\geq 1/100$ and $<1/10$), uncommon ($\geq 1/1000$ and $<1/100$), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Common: Thrombocytopenia

Immune system disorders

Uncommon: Anaphylactic response

Metabolism and nutrition disorders

Common: Hyperbilirubinaemia, Hypokalaemia, Electrolyte imbalance including blood potassium increased, blood magnesium decreased

Nervous system disorders

Common: Headache, Tremor

Uncommon: Convulsion, Neuropathy

Not known: Encephalopathy

Cardiac disorders

Common: Tachycardia, Cardiac Arrhythmias

Uncommon: Cardiac arrest

Vascular disorders

Common: Hypertension, Hypotension

Uncommon: Shock

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea, Asthma

Uncommon: Respiratory failure

Not known: Bronchospasm

Gastrointestinal disorders

Common: Nausea, Vomiting, Abdominal pain

Hepatobiliary disorders

Common: Liver function tests abnormal

Skin and subcutaneous tissue disorders

Common: Rash

Uncommon: Pruritus

Not known: Dermatitis exfoliative

Musculoskeletal and connective tissue disorders

Uncommon: Myalgia

Renal and urinary disorders

Common: Renal impairment including renal failure

Not known: Hyposthenuria, Renal tubular acidosis

General disorders and administration site conditions

Very common: Chills, Pyrexia

Uncommon: Injection site reaction

Investigations

Very common: Blood creatinine increased

Common: Blood alkaline phosphatase increased, blood urea increased

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 3.4). 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, hyperalimantation, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

3.9 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 3.8). 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.

4. PHARMACOLOGICAL 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.

4.1 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 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. PRECAUTIONS FOR STORAGE

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

6. PRECAUTIONS FOR 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 20ml 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 1mg/ml. For paediatric patients and patients with cardio-vascular disease the drug may be diluted with 5.0% Dextrose for Injection to a final infusion concentration of 2mg/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.