

AMPHOCIL™

Amphotericin B lipid complex

WHAT YOU SHOULD KNOW ABOUT AMPHOCIL

The information in this leaflet applies only to your medicine, AMPHOCIL, please read it carefully. It gives you important information but it can't tell you everything. If you have any questions or are not sure about anything ask your doctor or pharmacist.

WHAT IS YOUR MEDICINE?

AMPHOCIL is available as powder which is made up in sterile water for intravenous infusion (an injection into one of your veins, which is given over a period of time). AMPHOCIL vials contain either 50 mg or 100 mg of amphotericin B lipid complex.

Each infusion contains a number of inactive ingredients which allow it to be made. These are disodium edetate, lactose, sodium cholesteryl sulphate, tromethamine and hydrochloric acid.

AMPHOCIL comes in containers of 50 mg and 100 mg vials.

AMPHOCIL belongs to a group of medicines called antifungal antibiotics. This means that within the body it can kill a wide range of fungi which may be the cause of serious infections.

WHO HAS MADE YOUR MEDICINE?

The product licence holder of AMPHOCIL is:

Beacon Pharmaceuticals Ltd., 85 High Street, Tunbridge Wells, TN1 1YG, UK

AMPHOCIL is manufactured by:

Penn Pharmaceuticals Ltd., Gwent, NP2 3AA, UK

WHAT IS YOUR MEDICINE FOR?

AMPHOCIL is used to treat serious fungal infections, which can occur throughout the body. It is used when other similar treatments have not been successful or have caused unacceptable adverse experiences.

WHEN SHOULD AMPHOCIL NOT BE USED?

Before receiving your medicine, you should tell your doctor if you have ever had any reaction to amphotericin B or any of the inactive ingredients (as listed above).

These infusions should not be given to anyone other than the patient for whom they are prescribed.

WHAT PRECAUTIONS SHOULD BE TAKEN WITH AMPHOCIL?

Before receiving your medicine, tell your doctor if:

- You have any other medical problems, especially any problems with your kidneys;
- You are pregnant or suspect you are pregnant;
- You are breast feeding;
- You are diabetic, since AMPHOCIL contains a sugar additive, lactose, which may alter the control of your diabetes;
- You are taking any other medicines including those which you have bought. In particular, if you are taking steroid tablets or receiving steroid injections (for such conditions as asthma or rheumatism), tablets for heart failure (such as digoxin), or treatment for cancer (e.g. cisplatin), pentamidine, digitalis glycosides, muscle relaxants or other anti fungal drugs (such as flucytosine).



TECHNICAL LEAFLET

Issued to the Medical Profession Only

AMPHOCIL™

Amphotericin B lipid complex

TRADE NAME OF THE MEDICINAL PRODUCT

Amphocil™

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ingredient	Specification Reference	Quantity (W/W)
Amphotericin B	USP	5.060
Sodium cholesteryl sulphate	House	2.672
Tromethamine	USP	0.571
Disodium edetate	Ph. Eur.	0.034
Lactose, monohydrate	Ph. Eur.	91.311
Hydrochloric acid	Ph. Eur.	0.353 ^a
Water for injection	Ph. Eur.	^b
Nitrogen	NF	^c

^a HCl qs to a target pH of 7.0 ± 0.5

^b Mean NMT 2.0% residual moisture and no individual vial greater than 2.5%

^c Used to fill vial headspace

PHARMACEUTICAL FORM

Amphotericin B USP, 5% (W/W), lyophilisate for reconstitution. Each vial contains either 50 mg (50,000 IU) or 100 mg (100,000 IU) of amphotericin B USP as a lipid complex with sodium cholesteryl sulphate.

CLINICAL PARTICULARS

Therapeutic indications

AMPHOCIL is indicated for the treatment of severe systemic and/or deep mycoses in cases where toxicity or renal failure precludes the use of conventional amphotericin B in effective doses, and in cases where prior systemic antifungal therapy has failed. Fungal infections successfully treated with AMPHOCIL include disseminated candidiasis and aspergillosis. AMPHOCIL has been used successfully in severely neutopenic patients. AMPHOCIL is not intended for use in common, clinically inapparent fungal diseases diagnosed only by skin tests or serological determinations.

Posology and method of administration

Dosage: Therapy may begin at a daily dose of 1.0 mg/kg of body weight increasing to the recommended dose of 3.0-4.0 mg/kg as required. Doses as high as 6 mg/kg have been used in patients. Dosage should be adjusted to the individual requirements of each patient. The median cumulative dose in clinical studies was 3.5 g and the median treatment duration was 16 days. Ten percent (10%) of patients received 13 g or more of AMPHOCIL over a period of 27 to 409 days.

Administration: AMPHOCIL is administered by intravenous infusion at a rate of 1 to 2 mg/kg/hour. If the patient experiences acute reactions or cannot tolerate the infusion volume, the infusion time may be extended. Pre-medication (e.g. paracetamol, antihistamines, antiemetics) may be administered to patients who have previously suffered infusion related reactions.

Paediatric patients: A limited number of paediatric patients have been treated with AMPHOCIL at daily doses (mg/kg) similar to those in adults. No unusual adverse events were reported.

Elderly patients: A limited number of elderly patients have been treated with AMPHOCIL: available data do not indicate the need for specific dose recommendations or precautions in elderly patients.

Contraindications

AMPHOCIL should not be administered to patients who have documented hypersensitivity to any of its components, unless, in the opinion of the physician, the advantages of using AMPHOCIL outweigh the risks of hypersensitivity.

Special warnings and precautions for use

A test dose, which is advisable when commencing all new courses of treatment, should immediately precede the first dose: a small amount of drug (e.g. 20ml of a solution containing 0.1 g per litre) should be infused over 10 minutes and the patient carefully observed for the next 30 minutes.

In the treatment of diabetic patients: It should be noted that each vial of AMPHOCIL contains lactose monohydrate.

In the treatment of renal dialysis patients: AMPHOCIL should be administered only at the end of each dialysis period. Serum electrolytes, particularly potassium and magnesium, should be regularly monitored.

Interactions with other medicaments and other forms of Interaction

There have been no reported interactions between AMPHOCIL and other drugs including cyclosporine. However, caution should be used in patients receiving concomitant therapy with drugs known to interact with conventional amphotericin B such as nephrotoxic drugs (aminoglycosides, cisplatin and pentamidine), corticosteroids and corticotrophin (ACTH) that may potentiate hypokalaemia, and digitalis glycosides, muscle relaxants and antiarrhythmic agents whose effects may be potentiated in the presence of hypokalaemia.

The use of flucytosine with AMPHOCIL has not been studied. While the synergy between amphotericin B and flucytosine has been reported, amphotericin B may enhance the toxicity of flucytosine by increasing its cellular uptake and impeding its renal excretion. Acute pulmonary reactions have been noted in patients receiving amphotericin B during or shortly after leukocyte transfusions.

Pregnancy and use during lactation

Pregnancy: Animal reproductive toxicology studies with AMPHOCIL have shown no evidence of harm to the foetus. Although the active ingredient, amphotericin B, has been in wide use for many years without apparent ill consequence, there is inadequate evidence of safety of AMPHOCIL in human pregnancy. Therefore, it is recommended that administration of AMPHOCIL is avoided in pregnancy unless anticipated benefit to the patient outweighs the potential risk to the foetus.

Nursing mothers: It is not known whether amphotericin B is excreted in human milk. Consideration should be given to discontinuation of nursing during treatment with AMPHOCIL.

Effects on the ability to drive and use machines

Not applicable to current indication or expected use.

Undesirable effects

In general, the physician should monitor the patient for any type of adverse event associated with conventional amphotericin B. The appearance of adverse reactions does not generally prevent the patient completing the course of treatment. Caution should be exercised when high doses or prolonged therapy is indicated.

Acute reactions including fever, chills and rigours may occur. Anaphylactoid reactions including hypotension, tachycardia, bronchospasm, dyspnoea, hypoxia and hyperventilation have also been reported. Most acute reactions are successfully treated by reducing the rate of infusion and prompt administration of antihistamines and adrenal corticosteroids. Serious anaphylactoid effects may necessitate discontinuation of AMPHOCIL and treatment with additional supportive therapy (e.g. adrenaline).

Clinical studies conducted so far have shown AMPHOCIL to be less nephrotoxic than conventional amphotericin B. Serum creatine levels tend to remain consistent throughout the course of therapy even in patients with renal insufficiency. Patients who developed renal insufficiency during treatment with conventional amphotericin B were stabilised or improved when AMPHOCIL was substituted. Decreases in renal function attributable to AMPHOCIL treatment were rare. However, as with conventional amphotericin B, renal function should be monitored with particular attention to those patients receiving concomitant therapy with nephrotoxic drugs.

There have been no reports of unequivocal hepatic toxicity of AMPHOCIL. Changes in alkaline phosphatase and bilirubin levels were infrequent.

Changes in coagulation, thrombocytopenia and hypomagnesaemia were sometimes observed on AMPHOCIL. Anaemia, which is a very common adverse event during treatment with conventional amphotericin B, developed in only 2.5% of the patients treated with AMPHOCIL.

Other reported events included: nausea, vomiting, hypertension, headache, backache, diarrhoea and abdominal pain.



Your infusion is unlikely to adversely affect your ability to drive a car or to operate machinery.

This product is unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

Your infusion should not be mixed with or added to solutions containing other drugs.

HOW WILL I RECEIVE MY AMPHOCIL?

- AMPHOCIL will normally be given to you by your doctor or by a nurse
- AMPHOCIL is administered by intravenous infusion (directly into your blood) usually over a period of 2 to 4 hours. The exact dose you are given will be decided by your doctor.
- The dose range for AMPHOCIL is usually decided by using your body weight as a guide. Usually the starting daily dose is 1.0 mg/kg body weight increasing to the recommended dose of 3.0 to 4.0 mg/kg.
- If an infusion is missed, it should be given as soon as possible. Two infusions should not normally be given at the same time.
- If you are accidentally given more than your prescribed dose, your doctor will know to treat you accordingly.

WHAT UNDESIRABLE EVENTS MAY BE EXPERIENCED WITH AMPHOCIL?

As with all medicines, undesirable events are sometimes experienced. The following effects have been noted with AMPHOCIL:-

Fever (high temperature) and chills (feeling cold)

Feeling faint

Nausea or vomiting

Shortness of breath

Rapid heart beat

Abdominal pain

Back pain

Diarrhoea

Headache

Occasionally, AMPHOCIL may be associated with changes in your blood which may require your doctor to do certain blood tests. Do not be alarmed by the possibility of such events. You may not have any.

Tell your doctor or pharmacist if you experience any problems with your treatment.

HOW SHOULD I STORE AMPHOCIL?

Store below 30°C. The vials will normally be stored for you by the hospital. The staff are responsible for the correct storage, use and disposal of AMPHOCIL.

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Date of last revision:



Overdose

In case of overdose, stop administration immediately and carefully monitor the patient's clinical status (renal, liver and cardiac function, haematological status, serum electrolytes) and institute symptomatic treatment.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Amphotericin B is a macrocyclic polyene fungicidal antibiotic isolated from *Streptomyces nodosus*. Amphotericin B has a high affinity for ergosterol, the primary sterol in fungal cell membranes, and a lesser affinity for cholesterol, the predominant sterol of mammalian cell membranes. Binding of amphotericin B to ergosterol results in damage to the fungal cell membrane, enhanced membrane permeability and eventual cell death. Mammalian cell membranes also contain sterols, and it has been suggested that the damage caused by amphotericin B to human cells follows a similar mode of action to that of fungal cells. AMPHOCIL is considered to have the same mode of action as conventional amphotericin B, but with reduced toxicity.

AMPHOCIL is a novel formulation of amphotericin B based on its unique affinity for sterols. AMPHOCIL is a stable complex of amphotericin B and sodium cholesteryl sulphate, a naturally occurring cholesterol metabolite. Amphotericin B and sodium cholesteryl sulphate are complexed in a near equimolar ratio to form uniform disc-shaped microparticles. AMPHOCIL is not a liposomal formulation that encapsulates the amphotericin but a colloidal dispersion of amphotericin B and sodium cholesteryl sulphate. The two components form a disc-shaped bilayer, with amphotericin B forming a shield at the disc edges.

Pharmacological studies indicated that overall, AMPHOCIL is essentially equivalent, *in vitro*, to conventional amphotericin B against a variety of fungal pathogens. Higher doses of AMPHOCIL are tolerated, thus it is generally more effective in eradicating fungal infections than conventional amphotericin B in several *in vivo* models.

Pharmacokinetic properties

Pharmacokinetic studies in animals demonstrate that the distribution of AMPHOCIL and conventional amphotericin B are notably different. Lower peak plasma levels of amphotericin B and greater total area under the curve values after AMPHOCIL treatment, compare to comparable doses of conventional amphotericin B, have been observed. Higher concentrations of amphotericin B measured in the liver, spleen and bone marrow after AMPHOCIL administration were not accompanied by evidence of increased toxicity in these organ systems. Levels in the kidney, a primary site of toxicity of conventional amphotericin B, were 4- to 5-fold lower after treatment with AMPHOCIL and correlated with reduced nephrotoxicity compared to conventional amphotericin. Maximum plasma concentrations of amphotericin B were lower in AMPHOCIL treated animals. The terminal half-life was longer in the AMPHOCIL treated animals owing to the accumulation of amphotericin B in the liver and its subsequent slow release.

In bone marrow transplant patients administered AMPHOCIL at doses of 0.5 to 8.0 mg/kg, there was an increase in both the volume of distribution (V_{SS}) and the total plasma clearance (Cl) as the dose escalated. The mean values for V_{SS} , Cl, and terminal half-life for doses \leq 2.0 mg/kg were 2.25 l/kg, 0.0855 l/h/kg and 22.1 hours respectively. The mean values for doses $>$ 2.0 mg/kg were 3.61 l/kg, 0.116 l/h/kg and 27.2 hours respectively. The maximum steady-state concentrations achievable after multiple dosing ranged from 658 to 6212 μ g/l for doses of 0.5 to 8.0 mg/kg respectively. There was no evidence of continued accumulation of AMPHOCIL at doses of 8.0 mg/kg/day. There was no net change in renal function over the duration of AMPHOCIL treatment (range from 1 to 108 days, median 28 days).

Preclinical safety data

AMPHOCIL was found to be generally less toxic than conventional amphotericin B in a series of acute and repeat dose studies, with a 4 to 5 fold increased margin of safety. There were no unique toxicities observed following treatment with AMPHOCIL relative to conventional amphotericin B. Nephrotoxicity was diminished during AMPHOCIL treatment even at dose levels 4 to 5 fold higher than toxic doses of conventional amphotericin B. Accumulation of amphotericin B in the liver following AMPHOCIL administration was observed; however, there were no associated signs of increased hepatotoxicity relative to conventional amphotericin B. *In vitro* and *in vivo* tests on induction of gene and chromosome mutations were negative for amphotericin B. Carcinogenicity studies have not been conducted with amphotericin B or AMPHOCIL. To date there have been no clinical reports of carcinogenicity associated with the use of amphotericin B. Embryo-foetal studies in rats and rabbits, at doses of 2.5 mg/kg/day or greater showed maternal toxicity i.e. reduced weight gain and loss of appetite. There

were adverse effects on embryo-foetal development up to 10 mg/kg/day. There are no specific data for the effect of AMPHOCIL on human fertility, but in multiple dose toxicity studies of up to 13 weeks (in rats and dogs) there was no effect on ovarian or testicular histology. Although amphotericin B has not been associated with peri- or post-natal effects, no studies with AMPHOCIL are available.

PHARMACEUTICAL PARTICULARS

List of excipients

The following excipients are contained in each vial of lyophilised product: Sodium cholesteryl sulphate, Tromethamine, USP, Edentate disodium, Ph. Eur., Hydrochloric Acid, Ph. Eur., Water for injection, Ph. Eur., Lactose monohydrate, Ph. Eur.

Incompatibilities:

DO NOT RECONSTITUTE LYOPHILISED POWDER/CAKE WITH SALINE OR DEXTROSE SOLUTIONS. DO NOT ADD SALINE OR ELECTROLYTES TO THE RECONSTITUTED CONCENTRATE, OR MIX WITH OTHER DRUGS.

If administered through an existing intravenous line, flush with 5% Dextrose for Injection prior to infusion of AMPHOCIL, otherwise administer via a separate line.

The use of any solution other than those recommended, or the presence of a bacteriostatic agent (e.g., benzyl alcohol) in the solution, may cause precipitation of AMPHOCIL.

Do not use material that shows evidence of precipitation or any other particulate matter. Strict aseptic technique should always be followed during reconstitution and dilution since no preservatives are present in the lyophilised drug or in the solutions used for reconstitution and dilution.

Shelf-life

Unopened lyophilised material should be stored below 30°C. After reconstitution, the drug should be refrigerated at 2-8°C and used within 24 hours. Do not freeze. After further dilution with 5% Dextrose for Injection, the infusion should be stored in a refrigerator (2-8°C) and used within 24 hours. Partially used vials should be discarded.

Special precautions for storage

Store below 30°C.

Nature and contents of container

The container is Type I moulded glass vial, the stopper is a grey butyl lyophilisation type stopper, and the cap is an aluminium ring with either a green or yellow polypropylene flip-off top.

Instructions for use/handling

Directions for reconstitution and dilution: AMPHOCIL must be reconstituted by addition of sterile Water for Injection, Ph Eur, using a sterile syringe and a 20-gauge needle.

Rapidly inject into the vial:

50 mg/vial – 10 ml sterile Water for Injection

100 mg/vial – 20 ml sterile Water for Injection

Shake gently by hand, rotating the vial, until the yellow fluid becomes clear. Note that the fluid may be opalescent. The liquid in each reconstituted vial will contain 5 mg of amphotericin B per ml. For infusion, further dilute to a final concentration of 0.625 mg/ml by diluting 1 volume of the reconstituted AMPHOCIL with 7 volumes of 5% Dextrose for Injection.

Package quantities: Each vial of AMPHOCIL contains 50 mg or 100 mg of amphotericin B. The vials are packaged individually or in boxes of 10 vials each.

LEGAL CATEGORY: POM

MARKETING AUTHORISATION HOLDER:

Beacon Pharmaceuticals Ltd., 85 High Street, Tunbridge Wells, TN1 1YG, UK

Date of last revision:

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