

FOR THE USE ONLY OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY.

Amphotericin B Emulsion

अम्फोमुल
AMPHOMUL™



DESCRIPTION:

AMPHOMUL (Amphotericin B Emulsion) is a sterile, yellow coloured liquid for intravenous infusion containing Amphotericin B suspended in an oil-in-water emulsion base.

Amphotericin B is a polyene, antifungal antibiotic produced from a strain of *Streptomyces nodosus*. Amphotericin B has a molecular weight of 924.10 with a molecular formula of $C_{47}H_{73}NO_{17}$.

COMPOSITION:

Each ml contains:

Amphotericin B I.P., 5 mg

In a vehicle containing Soybean oil U.S.P., Glycerin I.P., Purified Egg Lecithin, Sodium Hydroxide I.P. and Water for Injection I.P.

THERAPEUTIC INDICATIONS:

AMPHOMUL is indicated for the treatment of:

- Visceral leishmaniasis (Kala Azar).
- Febrile neutropenia in Cancer Patients.

MICROBIOLOGY:

Mechanism of Action:

The active component of **AMPHOMUL** Amphotericin B, acts by binding to sterols in the cell membrane of susceptible fungi, with a resultant change in the permeability of the membrane.

Activity in vivo:

AMPHOMUL is active in murine animal model against *Disseminated Candidiasis and mouse sepsis model with Candida albicans*. End-points were clearance of microorganisms from target organ(s) and/or prolonged survival of infected animals.

PHARMACODYNAMIC PROPERTIES:

AMPHOMUL is an oil-in-water emulsion containing Amphotericin B. Amphotericin B is a macrocyclic, polyene antifungal antibiotic produced by *Streptomyces nodosus*. After administration of **AMPHOMUL**, Amphotericin B gets released from the oily phase in the monomeric form which is less toxic compared to oligomeric form contained in conventional formulation.

A strong interaction between Amphotericin B and oil droplets forms a reservoir of the monomeric form of Amphotericin B.

The monomeric form of Amphotericin B from **AMPHOMUL** has more affinity towards parasite cell wall, hence, binds strongly to the parasite cells inducing lethality. However, the same monomeric form of Amphotericin B has less affinity with cholesterol of mammalian cells and hence less toxic to the mammalian cells.

PRECLINICAL DATA:

In rodents, **AMPHOMUL** is at least 80-fold less toxic than conventional desoxycholate formulation of Amphotericin B when studied for toxicity.

AMPHOMUL gets distributed rapidly into the reticulo-endothelial System (RES) and hence a rapid build-up of Amphotericin B concentration is achieved in liver and spleen which are the target organs in patients of Visceral leishmaniasis (Kala Azar).

DESCRIPTION OF CLINICAL STUDIES:

Four clinical studies supporting the efficacy and safety of **AMPHOMUL** were conducted. This clinical program included both controlled and uncontrolled studies. These studies were carried out on patients with Visceral leishmaniasis and Cancer patients with febrile neutropenia.

Treatment of Visceral Leishmaniasis:

AMPHOMUL was studied for safety and efficacy in visceral leishmaniasis patients infected with *Leishmania donovani*.

AMPHOMUL achieved high rates of acute parasite clearance in patients when total doses of 9 - 15 mg/kg were administered. Most of these patients remained relapse-free during follow-up periods of 6 months or longer. Efficacy is expressed as both acute parasite clearance at the end of therapy (EOT) and as overall success (clearance with no relapse) during the follow-up period (F/U) of greater than 6 months for patients.

Empirical Therapy in Febrile Neutropenia Patients

In an open label multi-center trial, the efficacy of **AMPHOMUL** (5 mg/kg/day) was evaluated for the empirical treatment of 40 adult and pediatric neutropenic patients who were febrile despite having received at least 96 hours of broad spectrum antibacterial therapy. Therapeutic success required (a) resolution of fever during the neutropenic period, (b) absence of an emergent fungal infection, (c) patient survival for at least 7 days post therapy, (d) no discontinuation of therapy due to toxicity or lack of efficacy, and (e) resolution of any study-entry fungal infection.

AMPHOMUL, administered as an IV infusion over a period of 2 to 4 hours at a dosage of 5 mg/kg body weight showed better efficacy in febrile neutropenic cancer patients with definite/probable/presumptive fungal infection. Overall **AMPHOMUL** had shown favorable outcome in febrile neutropenic cancer patients with definite or probable or presumptive fungal infection. Very few breakthroughs in the fungal infection were observed during the study. More than 50% patients survived for 7 days beyond end of therapy.

The study demonstrated efficacy and safety of **AMPHOMUL** in the treatment of febrile neutropenia. Overall **AMPHOMUL** emulsion was well tolerated with very low incidence of nephrotoxicity and infusion related AEs.

The summary of all the four studies are as follows:

Study No.	Study Code	Number of Subjects	Treatment Arms	Key Findings
1.	SCP/BSV/KLZ/0102 (Kala Azar)	48	2 MKD x 7 days. 3.5 MKD x 4 alternate days. 5 MKD x 3 alternate days.	97% apparent cure rate seen. 93.75% definitive cure rate seen. The drug showed good tolerability.
2.	SCP/BSV/KLZ/0903 (Kala Azar)	45	5 MKD x 3 days. 4 MKD x 3 days. 3 MKD x 3 days.	Nearly 100% apparent cure rate and 91.11% definitive cure rate seen, no finding suggestive of higher efficacy using a higher MKD regimen. No incidence of drug-related hepatotoxicity or nephrotoxicity in the study is suggestive of better safety profile of the drug.
3.	BSV-AMBE II-0405 (Febrile Neutropenia)	40	5 MKD x 28 days (maximum).	The study demonstrated efficacy and safety of AMPHOMUL in the treatment of febrile neutropenia. Overall AMPHOMUL emulsion was well tolerated with very low incidence of nephrotoxicity and infusion related AEs.
4.	BSV-AMBE II-KA-0706 (Kala Azar)	60	7.5 mg/kg on Day 1 and Day 3. 10 mg/kg on Day 1 and 5 mg/kg on Day 3. 12.5 mg/kg on Day 1 and 2.5 mg/kg on Day 3. 15 mg/kg on Day 1.	Apparent cure 100% Definitive cure 93.33% Apparent cure 100% Definitive cure 73.33% Apparent cure 86.67% Definitive cure 80% Apparent cure 100% Definitive cure 100%
5.	BSV-AMBE III-KA-0908 (Kala Azar)	AMPHOMUL arm - 375 patients AmBisome arm - 125 patients	AMPHOMUL : 15mg/kg single dose on Day 1. AmBisome: 15mg/kg single dose on Day 1.	In the PP population, Initial cure at day 30/45 was 100% in both arms. Definitive cure rates at 180 days were 98.6% and 99% for AMPHOMUL and AmBisome respectively.

MKD mg/kg/day.

DOSAGE AND ADMINISTRATION:**Dosage:**

The recommended daily dosage for adults and children is 5 mg/kg given as a single infusion, administered intravenously at a rate of about 2.5 mg/kg/hour.

For Kala Azar:

The recommended total dose for adults and children for the treatment of Visceral Leishmaniasis (Kala Azar) is 15mg/kg and can be administered in any one of the following dosing regimen:

1. A single dose of 15mg/kg/day administered over a period of 4 hours (not recommended for children below 5 years of age)
2. A dose of 5mg/kg/day on three alternate days.
3. A dose of 7.5mg/kg/day on two alternate days.

For Febrile neutropenia:

The recommended dose is 5 mg/kg/day.

Administration:

AMPHOMUL should always be mixed with 5% Dextrose Injection and administered as an infusion mixture. The recommended concentration for intravenous infusion is 0.5 mg/ml to 2 mg/ml.

Preparation of infusion mixture - Shake the vial gently and withdraw the contents from the vials into one or more 10 / 20ml syringes using 18 gauge needle. Remove the needle from each syringe filled with **AMPHOMUL**. Attach to the syringe the 5µ syringe filter provided with each vial pack and then fix the 18 gauge needle to the other end of the syringe filter. Insert the needle into an I.V. bag containing 5% Dextrose Injection and empty the contents of the syringe into the bag. Shake the bag until the contents are thoroughly mixed.

Do not use the infusion mixture if there is any visible evidence of foreign matter.

Aseptic technique must be strictly observed throughout handling of **AMPHOMUL**, since no preservative is present in **AMPHOMUL**.

AMPHOMUL vials are for single use and hence any unused product should be discarded from the used vials.

DO NOT DILUTE **AMPHOMUL** WITH SODIUM CHLORIDE INJECTION (SALINE) OR MIX WITH OTHER DRUGS OR ELECTROLYTES.

DO NOT USE AN ON-LINE MICROBIAL FILTER (0.2µ Pore Size).

DURING ADMINISTRATION OF **AMPHOMUL** MIXTURE FOR INFUSION, GENTLY SHAKE THE CONTENTS OF THE INFUSION BAG EVERY ONE HOUR FOR PROPER MIXING.

IT IS NOT ADVISABLE TO STORE **AMPHOMUL** MIXTURE FOR INFUSION.

During administration of **AMPHOMUL**, serum creatinine level should be measured to monitor the renal toxicity. Dose adjustments should be made only after taking into account the overall clinical condition of the patient.

CONTRA-INDICATIONS:

AMPHOMUL is contra-indicated in patients who have shown hypersensitivity to Amphotericin B or any other component included in the formulation.

WARNINGS:

Anaphylaxis has been reported with the administration of Amphotericin B containing preparations. If severe respiratory distress occurs the infusion should be immediately discontinued and the patient should not receive further infusions of **AMPHOMUL**.

PRECAUTIONS:

AMPHOMUL should be administered under close clinical observation. Fever and chills may occur 1-2 hours after administration of **AMPHOMUL**.

Amphotericin B is known to cause sometimes hyperpnoea, respiratory stridor and modest hypotension. True bronchospasm or anaphylaxis is rare. As a precautionary measure, a test dose of **AMPHOMUL** equivalent to 1 mg of Amphotericin B is always recommended to be infused slowly. The patients should be observed for 2 hours prior to infusing the usual therapeutic dose.

Serum creatinine should be monitored during **AMPHOMUL** therapy. It is also advisable to regularly monitor liver function, blood count and serum magnesium and potassium content.

DRUG INTERACTIONS:

Amphotericin B is known to interact with the following drugs, which should be thus administered with caution.

Since nephrotoxic effects may be additive, the concurrent or sequential use of **AMPHOMUL** and other drugs with similar toxic potentials (e.g., aminoglycosides, capreomycin, colistin, cisplatin, cyclosporine, methoxyflurane, pentamidine, polymyxin B, vancomycin) should be avoided, if possible. Intensive monitoring of renal function is recommended if **AMPHOMUL** is used concomitantly with any of the known nephrotoxic drugs.

AMPHOMUL can interact with following drugs: Antineoplastic agents (concurrent use may enhance potential for renal toxicity), Corticosteroids and ACTH (may potentiate hypokalemia), Digoxin (Nephrotoxicity may decrease digoxin clearance and hypokalemia can potentiate toxicity of digoxin), Leukocyte transfusions (acute pulmonary toxicity if given concurrently), Zidovudine (increased myelosuppression and nephrotoxicity).

AMPHOMUL may potentiate the effects of skeletal muscle relaxants due to hypokalemia.

PREGNANCY AND LACTATION:

AMPHOMUL should only be used during pregnancy or breast feeding if the possible benefits to be derived outweigh the potential risks involved.

It is not known if **AMPHOMUL** is excreted in human milk.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

The clinical condition of most patients treated with **AMPHOMUL** precludes driving vehicles or operating machinery.

UNDESIRABLE EFFECTS:

Fever and chills / rigors are the most commonly experienced infusion related reactions expected to occur during administration of **AMPHOMUL** when no premedication to prevent these reactions is provided. **AMPHOMUL** treated patients experienced a significantly lower incidence of infusion-related reactions.

OVERDOSE:

If overdose occurs, stop administration of **AMPHOMUL** immediately. Carefully monitor clinical symptoms, monitor renal and hepatic function, serum electrolytes and hematological parameters.

AMPHOMUL has a large safety margin over the clinical dosage recommended. However, the toxicity of **AMPHOMUL** due to overdose has not been studied.

INCOMPATIBILITIES:

AMPHOMUL should not be co-administered through the same I.V. catheter with blood or plasma; although the clinical significance is not known. In-vitro studies have shown that the globular component of the emulsion vehicle forms aggregates when it comes in contact with human plasma.

AMPHOMUL is incompatible with saline solution and other solutions containing electrolytes.

STORAGE CONDITIONS:

Intact vials of **AMPHOMUL** should be stored below 25°C, do not freeze and protect from direct exposure to light. Any unused material should be discarded.

PRESENTATION:

AMPHOMUL is available in single use 10ml vials containing 50 mg Amphotericin B. Each vial pack is provided with 5µ syringe filter and package insert.

Patent No.: US7053061, EP1313449.



Manufactured in India by :
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, Additional M.I.D.C., Ambernath (E) - 421 501



IN90009D3