SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

AMPHOMUL (Amphotericin B Emulsion 50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Each ml contains :

Amphotericin B U.S.P. ..... 5 mg

Qualitative arid Quantitative composition of Amphomul

Composition	Quantity /ml	Reference to Standards	Function
Amphotericin B	5.0	USP	Active ingredient
Soybean Oil	0.2	USP	Non-aqueous vehicle for dispersion of Amphotericin B
Purified Egg Lecithin	0.012	In-house	Tonicity adjustment
Glycerin	0.0225	USP	Emulsifying agent
Sodium Hydroxide	q.s. to adjust pH	USP	pH adjustment
Water for Injection	q.s.	USP	Aqueous phase for emulsion.

3. PHARMACEUTICAL FORM:

Dosage form: Injection

Description: Amphomul (Amphotericin B Emulsion) is a yellow opaque liquid, which settles on keeping and gets dispersed on mild shaking.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

AMPHOMUL is indicated for the treatment of:

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

4.2 Posology and method of 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 dose for adults and children is up to 15 mg/kg in divided doses. A dose of 5 mg/kg/day on three alternate days or a dose of 7.5 mg/kg/day on two

alternate days is recommended for the treatment of Visceral leishmaniasis (Kala Azar). In the controlled clinical trials, a single bolus dose of 15 mg/kg administered over a period of 4 hours has also been found to be effective in the treatment of Visceral leishmaniasis (Kala Azar).

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 fiiter. 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.

4.3 Contra-indications

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

4.4 Special warning and precautions for use

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 strider 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

4.5 Interaction with other drugs , other forms of 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.

4.6 Use in 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.

4.7 Effects on ability to drive and operate machine

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

4.8 Undesirable effects

Fever and chills *I* 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.

4.9 Overdoses

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

5. PHARMACOLOGICAL PROPERTIES:

Pharmaco-dynamic properties

Pharmacotherapeutic group: Anti-infectives for systemic use, ATC code: J02AA01

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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

- Soybean Oil

- Purified Egg Lecithin
- Glycerin
- Sodium Hydroxide

6.2 . Incompatibilities:

Do not mix with other IV medications.

6.3 Shelf-life:

24 months from the date of manufacturing.

6.4 Special precaution for storage:

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.

6.5 Nature and contents of container:

Amphomul will be marketed in USP Type I clear, colourless glass containers i.e. vials of 10 ml Capacity. **Amphomul** (Amphotericin B Emulsion) is packaged in USP Type I moulded flint Glass vial of 10 ml capacity. Filled labelled vials are blister packed in an aluminum foil and PVC film. Each blister is then placed in the carton along with the insert.

6.6 Special precautions for disposal

Not applicable

7. APPLICANT/MANUFACTURER:

Applicant:

Bharat Serums & Vaccines Ltd.
3rd Floor, Liberty Tower, Plot No. K-10,
Behind Reliable Plaza, Kalwa Industrial Estate, Airoli,
Navi Mumbai 400708

Manufactured by:

Bharat Serums and Vaccines Limited.
Plot No. K-27, Anand Nagar, Jambivili Village,
Additional M.I.D.C., Ambernath East- 421506,
Maharashtra State, India.