

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

**AMPHOTERICIN B LIPID COMPLEX INJECTION I.V.
AMPHOLIP**

DESCRIPTION :

Yellow coloured suspension, which settles on keeping and gets dispersed uniformly on mild shaking.

COMPOSITION :

Each ml of the suspension contains 5.0mg of Amphotericin B. Additionally it contains Dimyristoylphosphatidylcholine (DMPC), Dimyristoylphosphatidylglycerol (DMPG), Sodium Chloride and Water for Injection.

CLINICAL INFORMATIONS :

Clinical Indications :

Ampholip is indicated for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional Amphotericin B therapy.

Dosage and Administration :

Ampholip is a sterile, pyrogen-free suspension to be diluted for intravenous infusion only.

As for use with all Amphotericin B products, facilities for cardiopulmonary resuscitation should be readily at hand when administering **Ampholip**, due to the possible occurrence of anaphylactoid reactions.

For severe systemic infections treatment is generally recommended at 5.0 mg/kg for at least 14 days. **Ampholip** should be administered by intravenous infusion at a rate of 2.5 mg/kg/hr. An initial test dose of 1.0 mg should be infused intravenously over 15 minutes.

Ampholip should be mixed with 5% Dextrose Injection and administered as a 1mg/ml infusion mixture. However pediatric patients and patients with cardiovascular disease could be administered **Ampholip** as a 2mg/ml infusion mixture after diluting with 5% Dextrose Injection.

Preparation of infusion mixture - Shake the vial gently and withdraw required dose of Amphotericin B from the vials into one or more 20ml syringe using 18 gauge needle. Remove the needle from each syringe filled with **Ampholip** and replace with the 5µ filter needle supplied with each vial pack. Insert the filter needle of the syringe 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 evidence of foreign matter.

The infusion is best administered by means of an infusion pump.

Aseptic technique must be strictly observed throughout handling of **Ampholip**, since no preservative or bacteriostatic agent is present in Ampholip. Ampholip vials are for single use and hence any unused material should be discarded.

DO NOT DILUTE WITH SODIUM CHLORIDE INJECTION (SALINE) OR MIX WITH OTHER DRUGS OR ELECTROLYTES. DO NOT USE AN ON-LINE MICROBIAL FILTER.

DURING ADMINISTRATION OF AMPHOLIP MIXTURE (1mg/ml), MIX THE CONTENTS OF THE BAG BY SHAKING THE INFUSION BAG EVERY TWO HOURS.
IT IS NOT ADVISABLE TO STORE THE DILUTED **AMPHOLIP** INFUSION MIXTURE.

During administration of **Ampholip**, 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.

Ampholip has been administered for as long as 11 months, and cumulative doses have been as high as 56.6 g without significant toxicity.

Paediatric Use :

Systemic fungal infections in children have been treated successfully with **Ampholip** at doses comparable to the recommended adult dose on a body weight basis.

Use In Elderly Patients :

Systemic fungal infections in elderly patients have been treated successfully with **Ampholip** doses comparable to the recommended dose on a body weight basis.

Use In Neutropenic Patients :

Ampholip has been successfully used 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.

Contra-Indications :

Ampholip is contra-indicated in patients with known hypersensitivity to Amphotericin B or any of its components, unless in the opinion of the physician the advantages of using **Ampholip** outweigh the risks of hypersensitivity.

Special warnings and special precautions for use :

Systemic Fungal Infections :

Ampholip should not be used for treating common or superficial, clinically inapparent fungal infections that are detectable only by positive skin or serologic tests.

Renal Disease :

Since Amphotericin B is a potentially nephrotoxic drug, monitoring of renal function should be performed before initiating treatment in patients with pre-existing renal disease, and at least once weekly during therapy. **Ampholip** should be administered to patients undergoing renal dialysis only after the completion of dialysis. Serum potassium and magnesium levels should be monitored regularly.

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 **Ampholip**. In cases where serum bilirubin, alkaline phosphatase or serum transaminases increased, factors other than **Ampholip** were present and possibly accounted for the abnormalities. These factors included infection, hyperalimentation, concomitant hepatotoxic drugs and graft-versus-host disease.

Interactions with other medicaments :

Nephrotoxic Drugs :

Amphotericin B is a potentially nephrotoxic, 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 **Ampholip** was administered concomitantly with zidovudine. If concomitant treatment with zidovudine is required, renal and haematologic function should be closely monitored.

Cyclosporin :

Preliminary data suggest that patients receiving **Ampholip** concomitantly with high dose of cyclosporin experience an increase in serum creatinine. The data also suggest that the increase in serum creatinine is caused by cyclosporin and not by **Ampholip**.

Conventional Amphotericin B has been reported to interact with antineoplastic agents, corticosteroids and corticotrophin (ACTH), digitalis glycosides and skeletal muscle relaxants.

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 Amphotericin B in rats and rabbits showed no evidence of embryotoxicity, foetotoxicity or teratogenicity. However, safety for use in pregnant or lactating women has not been established for **Ampholip**. Therefore, **Ampholip** should be administered to pregnant or lactating women only for life-threatening disease when the likely benefit exceeds the risk to the mother and foetus.

Effect on Ability to Drive and Use Machines :

Ampholip is unlikely to affect the ability of an individual to drive or use machines, since adverse reactions are usually infusion-related. However, the clinical condition of patients who require **Ampholip** generally precludes driving or operating machinery.

Undesirable Effects :

Patients in whom significant renal toxicity was observed following conventional Amphotericin B frequently did not experience similar effects when **Ampholip** was substituted. Adverse reactions related to the administration of **Ampholip** have generally been mild or moderate, and have been most prevalent during the first 2 days of dosing.

Premedication (e.g. paracetamol) may be administered for the prevention of infusion related adverse events. The most common clinical adverse effects have been chills, fever, nausea and vomiting, which may occur during the first 2 days of treatment.

Decline in renal function, shown by increased serum creatinine, azotemia and hypokalaemia, have not typically required discontinuation of treatment. **Ampholip** has not been reported to directly cause changes in hepatic or haematologic function.

Adverse reactions that have been reported to occur with conventional Amphotericin B may occur with **Ampholip**. In general, the physician should monitor the patient for any type of adverse event associated with conventional Amphotericin B.

Overdose :

No serious acute reactions of cardio-respiratory arrest has been reported as found with the overdosage of Amphotericin B desoxycholate. If an overdosage is suspected, discontinue the therapy, monitor the patient closely and administer supportive therapy as required. **Ampholip** is not hemodialyzable.

PHARMACOLOGICAL INFORMATION :

Ampholip contains the antifungal agent, Amphotericin B, complexed with 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.

Pharmacodynamic properties :

Mechanism of action :

Amphotericin B, the active antifungal agent in **Ampholip**, may be fungistatic or fungicidal, depending on its concentration and on fungal susceptibility. The drug 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.

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 mg/ml. Amphotericin B has little or no activity against bacteria or viruses.

Pharmacokinetic Properties :

The pharmacokinetic properties of **Ampholip** and conventional formulation of Amphotericin B containing desoxycholate are different. Pharmacokinetic studies in animals showed that, after administration of **Ampholip**, Amphotericin B levels were higher in the liver and spleen. Amphotericin B in **Ampholip** was rapidly distributed to tissues. The ratio of drug concentrations in tissues to those in blood increased disproportionately with increasing dose, suggesting that elimination of the drug from the tissues was delayed. Peak blood levels of Amphotericin B were lower after administration of **Ampholip** than after administration of equivalent amounts of conventional drug. Administration of conventional Amphotericin B resulted in much lower tissue levels than did dosing with **Ampholip**.

The rapid clearance and large volume of distribution of **Ampholip** result in a relatively low AUC and are consistent with preclinical data showing high tissue concentrations. The kinetics of **Ampholip** are nonlinear.

Preclinical Safety Data :

Acute toxicity studies in rodents showed that **Ampholip** 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, **Ampholip** 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.

Carcinogenesis, Mutagenesis and Impairment of Fertility :

Since conventional Amphotericin B first became available, there have been no reports of drug-related carcinogenicity, mutagenicity, teratogenicity or adverse effect on fertility. **Ampholip** has been shown not to be mutagenic by the in vivo mouse micronucleus 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.

PHARMACEUTICAL INFORMATIONS :

Storage Conditions :

Ampholip should be stored under refrigeration at 2^oC to 8^oC. Do not freeze. Protect from direct exposure to light.

Presentation :

Single dose vials containing 2 ml (10 mg Amphotericin B), 10 ml (50 mg Amphotericin B) and 20 ml (100 mg Amphotericin B). Each vial is packed individually in a carton along with one 5µ filter needle and a pack insert.

Manufactured in India by :

BHARAT SERUMS AND VACCINES LIMITED

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