Amphotericin B, the active antifungal agent in **AMPHONEX**, may be fungistatic or fungicidal, depending on the concentration attained in body fluids and also on fungal susceptibility.

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 in concentrations of 0.03-1.0 mcg/ml. Amphotericin B has little or no activity against bacteria or viruses.

Pharmacokinetics:
At clinical doses of 1 to 7.5 mg/Kg, Liposomal Amphotericin B has been reported to produce peak plasma concentration of around 8 to 80 micrograms/mL, around 20 times more than that obtained with conventional formulation of Amphotericin B deoxycholate. No significant drug accumulation has been reported in the plasma following repeated administration of Liposomal Amphotericin B. Steady state was reached within four days of dosing. Volume of distribution on day 1 and at steady state suggests extensive tissue distribution of Liposomal Amphotericin B.

The metabolic pathway of Amphotericin B and Liposomal Amphotericin B are not known. Due to the size of the liposomes there is no glomerular filtration and renal elimination, thus avoiding the potential for nephrotoxicity.

Preclinical Safety Data:
Acute toxicity studies in rodents showed that **AMPHONEX** was 50-fold to 80-fold less toxic than conventional formulation of Amphotericin B deoxycholate.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Since conventional Amphotericin B first became available for clinical use, there have been no reports of drug-related carcinogenicity, mutagenicity, teratogenicity or adverse effect on fertility. Liposomal Amphotericin B has been reported to be non-mutagenic in bacterial and mammalian system. Liposomal Amphotericin B has also been reported to be non-teratogenic when tested in mice and rabbits.

When tested in rats Liposomal Amphotericin B has been reported to have no adverse effects on male and female reproductive functions.

PHARMACEUTICAL INFORMATION:
Shelf Life:
36 Months.

Storage Conditions:
Store below 25°C. Do not freeze.

Presentation:
Single dose vials containing 50mg Amphotericin B. Each vial is packed individually in a Carton along with one 5µ Syringe filter and a package insert.

Keep out of reach of children.

Manufactured in India by :
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, Additional M.I.D.C.,
Ambernath (E) - 421 501 IN90298E0EX

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

AMPHONEX

50 mg (Lyophilized)

Liposomal Amphotericin B Injection

For intravenous infusion to hospitalized patients only

DESCRIPTION:
AMPHONEX is a liposomal formulation containing Amphotericin B intercalated into the lipid bilayer. It is a lyophilized sterile product for intravenous infusion.

It is presented as yellow powder / cake requiring reconstitution before use.

COMPOSITION:
Each vial contains :
Amphotericin B Ph. Eur ..... 50 mg
Intercalated into liposomal membrane
Excipients ..... q.s.

Following reconstitution with Sterile Water for Injection the resulting pH of the dispersion is between 4.5-6.5.

Amphotericin B has molecular formula of $C_{47}H_{73}NO_{17}$ and molecular weight of 924.10.

CLINICAL INFORMATION:
Indications:
AMPHONEX is indicated in the treatment of:
i) Systemic mycotic infections due to organisms susceptible to Amphotericin B, where toxicity precludes the use of conventional systemic Amphotericin B therapy. Infections such as disseminated candidiasis, mucormycosis, aspergillosis, cryptococcosis, histoplasmosis have been successfully treated with Liposomal Amphotericin B.
ii) Fever of unknown origin in neutropenic patients where the fever has failed to respond to broad spectrum antibiotic therapy and appropriate investigations carried out have failed to establish the cause as bacterial or viral.
Iii) Visceral leishmaniasis in both adults and children.

Administration and Dosage:
Instruction for use:
Reconstitute each vial of **AMPHONEX** with 12mL of Water for Injection and shake the vial vigorously till a yellow uniform translucent solution is obtained. Amphotericin B content in this reconstituted solution is about 4mg/mL.

Withdraw from the vial, calculated volume of reconstituted product (4mg/mL) into a sterile syringe. Using the 5µ Syringe filter provided, instill the reconstituted product into a sterile container containing the calculated amount of 5% Dextrose Injection. Use 1 to 19 parts of Dextrose Injection for dilution to yield a solution between 2mg and 0.2mg Amphotericin B per mL.

To reconstitute the powder/cake, use only Sterile Water for Injection.

To dilute the reconstituted product, use only Dextrose Injection.

Like all other parenteral products, if there is any evidence of precipitation or foreign matter before or after dilution, do not administer the product.

Administration:
As for use with all Amphotericin B products, a test dose (1mg) should be administered slowly for upto 10 minutes keeping the patient under constant observation for 30 minutes. Proceed further with the administration of the required dose only after confirming that no serious anaphylactic or allergic reactions have occurred with the test dose.

Adults and Children:
AMPHONEX should be administered by intravenous infusion after diluting the reconstituted product to a concentration of Amphotericin B between 0.2mg-2mg/mL. The rate of administration should be carried out using controlled infusion device, over a period of approximately 120min. Infusion time may reduce to approximately 60 minutes in patients in whom the treatment is well tolerated.

Dosage:
For the treatment of systemic mycotic infection:
Institute the therapy at a daily dose of 1mg/kg body weight. Increase gradually to 3mg/kg. Accumulated dose of 1 to 3g of Amphotericin B as Liposomal Amphotericin B over 3 to 4 weeks is normally recommended.

For the treatment of fever of unknown origin in neutropenic patients:
For the treatment of fever of unknown origin in neutropenic patients, therapy should be initiated at 1mg/kg/day, the dose may be raised to 3mg/kg/day if required.

For the treatment of visceral leishmaniasis:
A total dose of 21 to 30mg/kg body weight given over 10 to 21 days is recommended. Alternatively, 3mg/kg/day for 10 days is recommended.

In immune compromised patients a dose of 1 to 1.5mg/kg/day for 21 days is recommended. Because of the risk of relapse, maintenance therapy or re-induction therapy is recommended.

Aseptic technique must be strictly observed throughout handling of **AMPHONEX**, since no preservative or bacteriostatic agent is present in the product. **AMPHONEX** vials are for single use. Any unused material after reconstitution should be discarded.

DO NOT DILUTE WITH SODIUM CHLORIDE INJECTION (SALINE) OR MIX WITH OTHER DRUGS OR ELECTROLYTES. DO NOT USE AN ON-LINE FILTER WITH PORE SIZE LESS THAN 1 MICRON.

Physical and chemical stability of the reconstituted product as well diluted infusion mixture has been found satisfactory upto 48 hours when stored below 25°C. However, it is advisable to use the infusion mixture of Liposomal Amphotericin B immediately after dilution as **AMPHONEX** contains no preservatives.

Paediatric Use:
Systemic fungal infections and fever of unknown origin in children have been treated successfully with **AMPHONEX** at doses comparable to the recommended adult dose on a body weight basis.

Use in Elderly Patients:
No adjustment in the recommended dose on a body weight basis is required.

Contra-Indications:
AMPHONEX 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 **AMPHONEX** outweigh the risks of hypersensitivity.

Special warnings and special precautions for use:
Anaphylactic reactions:
Anaphylactic reactions have been rarely reported during the intravenous administration of Liposomal Amphotericin B. As for use with all Amphotericin B products, facilities for cardiopulmonary resuscitation should be readily available at hand when administering **AMPHONEX**, due to the possible occurrence of anaphylactoid reactions.

Allergic type reactions can occur during administration of **AMPHONEX** like any other Amphotericin B containing products. Even though, infusion related reactions are not usually serious, prevention or treatment of these reactions as precautionary measures should always be considered. Slower infusion rate, dilution of the infusion mixture, administration of drugs like diphenhydramine, paracetamol, pethidine and/or hydrocortisone have been reported to be successful in the prevention or treatment of infusion related reactions.

AMPHONEX has been shown to be significantly less toxic than Amphotericin B deoxycholate; however, some of the adverse events have still been reported to occur.

During prolonged therapy of **AMPHONEX**, if the renal function deteriorates, the dose reduction / discontinuation of therapy should be considered until renal function improves. Any concomitant therapy with known nephrotoxic drugs should also be taken into account before dose reduction / discontinuation of therapy.

In the treatment of Diabetic Patients:
Each vial of **AMPHONEX** contains 900mg of Sucrose. Diabetic patients should be administered **AMPHONEX** only after considering sugar content in the vial.

Interactions with other medicaments:
No specific data on pharmacokinetic interaction studies are available after administration of **AMPHONEX.**

Nephrotoxic Drugs:
Amphotericn B is a potentially nephrotoxic drug and hence close monitoring of renal function in particular is required for patients receiving nephrotoxic drugs concomitantly. However, for patients receiving concomitant cyclosporine and/or aminoglycosides, **AMPHONEX** has been reported to be associated with significantly less nephrotoxicity as compared to Amphotericin B deoxycholate.

Concurrent administration of **AMPHONEX** with other nephrotoxic agents such as cyclosporine, polymixin, tacrolimus and aminoglycosides may increase the risk of nephrotoxicity in some patients.

Loop diuretics or thiazides and related diuretics have been reported to increase the risk of hypokalaemia when administered with Amphotericin B.

Pregnancy and Lactation:
Safety for use in pregnant or lactating women has not been established for **AMPHONEX.** 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. Therefore, **AMPHONEX** 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:
AMPHONEX 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 **AMPHONEX** generally precludes driving or operating machinery.

Undesirable Effects:
Patients in whom significant renal toxicity was observed following conventional Amphotericin B therapy frequently did not experience similar effects when Liposomal Amphotericin B was substituted. Adverse reactions related to the administration of Liposomal Amphotericin B 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 fever chills/rigors, which may occur during the first administration of Liposomal Amphotericin B.

Less frequent infusion related reactions include back pain and/or chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, and hypotension

Overdose:
If an overdosage is suspected, discontinue the therapy. Monitor the patient closely for renal and hepatic functions. Administer supportive therapy as required.

PHARMACOLOGICAL INFORMATION:
Pharmacodynamics:
AMPHONEX contains the antifungal agent, Amphotericin B, which is a macrocyclic, polyene, broad-spectrum antifungal antibiotic produced by Streptomyces nodosus.

Amphotericin B in Liposomal Amphotericin B is strongly associated with the bilayer structure of small unilamellar liposomes. Amphotericin B exerts its antifungal activity via binding to ergosterol in the fungal cell membrane. This disrupts cell permeability and results in rapid cell death.