SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal product:

1.1 Product name

Amphonex

(Liposomal Amphotericin B Injection) (Lyophilized)

1.2 Strength

50 mg / Vial

1.3 Pharmaceutical dosage form

Amphonex (Liposomal Amphotericin B Injection) (Lyophilized) is a freeze dried preparation of Amphotericin B for intravenous injection. Amphonex (Liposomal Amphotericin B Injection), Lyophilized is a yellow coloured cake.

2. Qualitative and Quantitative compositions

Qualitative and Quantitative composition of Amphonex Injection

Names of Ingredients	Quantity / vial	Function	Reference to Standards
Active Substance(s)			
Amphotericin B Lipid Powder@	Equivalent to 50 mg Amphotericin B	Active ingredient	I.H.
Excipient(s)			
Disodium Succinate Hexahydrate	27 mg	Buffering agent	I.H.
Sucrose	900 mg	Stabilizer	Ph.Eur
Water for Injection#	q.s. to 12.5 ml	Solvent	Ph.Eur

IH → In House

Ph. Eur → European Pharmacopoeia

q.s. → Quantity sufficient

does not remain in finished product

@ contains Amphotericin B Ph. Eur., hydrogenated soy Phosphatidylcholine (HSPC), di stearoyl phosphatidylglycerol sodium (DSPG-Na), cholesterol Ph.

Eur., Alpha-tocopherol Ph. Eur & hydrochloric acid Ph. Eur**.**

3. Pharmaceutical form:

Amphonex (Liposomal Amphotericin B Injection) (Lyophilized) is a yellow coloured lyophilized cake. **4. Clinical particulars:**

4.1 Therapeutic 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.

4.2 Posology and method of administration

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 reinduction 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.

4.3 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.

4.4 Special warning and 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.

4.5 Interaction with other drugs, other forms of interactions

No specific data on pharmacokinetic interaction studies are available after administration of **AMPHONEX**.

4.6 Use in 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 lifethreatening disease when the likely benefit exceeds the risk to the mother and foetus.

4.7 Effects on ability to drive and operate machine

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.

4.8 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.

4.9 Overdoses

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

5. Pharmacological properties :

5.1 Pharmaco-dynamic properties

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.

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.

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, antibiotics; ATC code: J02AA01

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.

5.2 Pharmaco-kinetic properties

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.

5.3 Pre-clinical studies

In an extensive range of animal toxicity studies studied in laboratory animal models (mice, rats), no significant findings were observed.

6. Pharmaceutical particulars :

6.1 List of excipients:

1. Disodium Succinate Hexahydrate I.H.
2. Sucrose Ph.Eur

3. Water for Injection Ph.Eur

IH - In-House

Ph.Eur - European Pharmacopoeia

6.2 Incompatibilities:

Do not mix with other IV medications.

6.3 Shelf-life:

36 months from the date of manufacturing.

6.4 Special precaution for storage:

Store below 25 ^{o}C. Do not freeze

6.5 Nature and contents of container:

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.

7. Marketing Authorization Holder :

Bharat Serums & Vaccines Ltd.
17th Floor, Hoechst House,
Nariman Point,
Mumbai – 400 021
India.

8. Marketing Authorization Number :

Not Applicable

9. Date of First Authorization / Renewal of Authorization :

Not Applicable

10. Date of revision of the text :

Not Applicable