Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Amphonex 50 mg

2. Qualitative and quantitative composition

Each vial contains:
Amphotericin B Ph. Eur.....50mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Lyophilized powder for Injection

Before Reconstitution: Yellow coloured cake.
After Reconstitution: Lyophilized cake disperses uniformly without any signs of agglomerates giving yellow translucent liquid.

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 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 25oC. However, it is advisable to use the infusion mixture of

Liposomal Amphotericin B immediately after dilution as AMPHONEX contains no preservatives.

4.3 Contraindications

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 warnings 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 medicinal products and other forms of interaction

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

4.6 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.

4.7 Effects 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.

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.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via National Pharmacovigilance Electronic Reporting Systems' to the respective National Regulatory Authorities.

4.9 Overdose

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 Pharmacodynamic 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.

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 Pharmacokinetic 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 Preclinical safety data

In subchronic toxicity studies in dogs (1 month), rabbits (1 month) and rats (3 months) at doses equal to or, in some species, less than the clinical therapeutic doses of 1 to 3 mg/kg/day, the target organs for L-AmB toxicity were the liver and kidneys with thrombocytopenia also observed. All are known targets for amphotericin B toxicity.

L-AmB was found to be non-mutagenic in bacterial and mammalian systems.

Carcinogenicity studies have not been conducted with L-AmB.

No adverse effects on male or female reproductive function were noted in rats.

6. Pharmaceutical Particulars

6.1 List of Excipients

Disodium Succinate Hexahydrate
Sucrose
Water for Injection

6.2 Incompatibilities

Do not mix with other IV medications.

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 25° C. Do not freeze.

6.5 Nature and Content 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.

6.6 Special precautions for disposal and other handling

READ THIS ENTIRE SECTION AND SECTION 4.4 CAREFULLY BEFORE BEGINNING RECONSTITUTION

Amphotericin B liposomal must be reconstituted using Sterile Water for Injection (without a bacteriostatic agent) and diluted in Dextrose solution (5%, 10% or 20%) for infusion only.

The use of any solution other than those recommended, or the presence of a bacteriostatic agent (e.g., benzyl alcohol) in the solution, may cause precipitation of Amphotericin B liposomal.

Amphotericin B liposomal is NOT compatible with saline and must not be reconstituted or diluted with saline or administered through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5%, 10% or 20%) for infusion. If this is not feasible, Amphotericin B liposomal should be administered through a separate line.

Do NOT mix Amphotericin B liposomal with other medicinal products or electrolytes.

Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in Amphotericin B liposomal, or in the materials specified for reconstitution and dilution.

Amphotericin B liposomal must be reconstituted by suitably trained staff.

Vials of Amphotericin B liposomal containing 50 mg of amphotericin B are prepared as follows:

If you need to reconstitute more than one vial, complete the whole reconstitution and dispersion process for one vial before adding the sterile water to the next vial.

. Add 12 ml of Sterile Water for Injection to the Amphotericin B liposomal vial, to yield a preparation containing 4 mg/ml amphotericin B.

2. IMMEDIATELY after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 seconds to completely disperse the Amphotericin B liposomal. After reconstitution the concentrate is a translucent, yellow dispersion. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained. Do not use if there is any evidence of precipitation of foreign matter.
3. Calculate the amount of reconstituted (4 mg/ml) Amphotericin B liposomal to be further diluted (see table below).
4. The infusion solution is obtained by dilution of the reconstituted Amphotericin B liposomal with between one (1) and nineteen (19) parts dextrose solution (5%, 10% or 20%) for infusion by volume, to give a final concentration in the recommended range of 2.00 mg/ml to 0.20 mg/ml amphotericin B as Amphotericin B liposomal (see table below).
5. Withdraw the calculated volume of reconstituted Amphotericin B liposomal into a sterile syringe. Using the 5 micron filter provided, instill the Amphotericin B liposomal preparation into a sterile container with the correct amount of dextrose solution (5%, 10% or 20%) for infusion.

An in-line membrane filter may be used for intravenous infusion of Amphotericin B liposomal. However, the mean pore diameter of the filter should not be less than 1.0 micron.

Example of the preparation of Amphotericin B liposomal dispersion for infusion at a dose of 3mg/kg/day in dextrose 5% solution for infusion.

Weight (kg)	Number of vials	Amount Amphotericin B liposomal (mg) to be withdrawn for further dilution	Volume of reconstituted Amphotericin B liposomal (ml)*	To make up a 0.2mg/ml concentration (1 in 20 dilution)		To make up a 2.0mg/ml concentration (1 in 2 dilution)	
				Volume of 5% dextrose needed (ml)	Total volume (ml; Amphotericin B liposomal plus 5% dextrose)	Volume of 5% dextrose needed (ml)	Total volume (ml; Amphotericin B liposomal plus 5% dextrose)
10	1	30	7.5	142.5	150	7.5	15
25	2	75	18.75	356.25	375	18.75	37.5
40	3	120	30	570	600	30	60
55	4	165	41.25	783.75	825	41.25	82.5
70	5	210	52.5	997.5	1050	52.5	105
85	6	255	63.75	1211.25	1275	63.75	127.5

* Each vial of Amphotericin B liposomal (50mg) is reconstituted with 12ml Water for Injection to provide a concentration of 4mg/ml amphotericin B.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

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

8. Marketing Authorization Number
H2016/CTD1130/866

9. Date of first authorization/renewal of the authorization
16/02/2017

10. Date of revision of the text
16th June, 2026