Summary of Product Characteristics

1. Name of the Medicinal product

AMPHONEX 50 mg (Liposomal Amphotericin B for Injection) (Lyophilized).

2. Qualitative and Quantitative compositions

Each vial contains 50 mg of amphotericin (50,000 units) encapsulated in liposomes

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Sterile Lyophilized powder for solution for intravenous infusion.

After reconstitution: Lyophilized cake disperses uniformly without any signs of agglomerates giving yellow translucent liquid.

4. Clinical particulars

1. Therapeutic indications

Amphonex is indicated in adults and children aged 1 month to 18 years old for:

- the treatment of severe systemic and/or deep mycoses
- the treatment of visceral leishmaniasis in immunocompetent patients including both adults and children
- the empirical treatment of presumed fungal infections in febrile neutropenic patients, where the fever has failed to respond to broad spectrum antibiotics and appropriate investigations have failed to define a bacterial or viral cause.

  Infections successfully treated include: disseminated candidiasis, aspergillosis, mucormycosis, chronic mycetoma, cryptococcal meningitis and visceral leishmaniasis.

  Should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.

- L-AmB should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.

2. Posology and method of administration

Non-equivalence of amphotericin products

Different amphotericin products (sodium deoxycholate, liposomal, lipid complex) are not equivalent in terms of pharmacodynamics, pharmacokinetics and dosing and so the products should not be used interchangeably without accounting for these differences. Both the trade name, common name and dose should be verified pre-administration.

There is a risk of under-dose if L-AmB is administered at a dose recommended for amphotericin B deoxycholate.

Posology:

Administration of a test dose is advisable before a new course of treatment. A small amount of an L-AmB infusion (e.g. 1 mg) can be administered for about 10 minutes and then stopped and the

patient observed carefully for the next 30 minutes. If there have been no severe allergic or anaphylactic/anaphylactoid reactions the infusion of L-AmB dose can be continued.

For the treatment of systemic mycoses:
Institute the therapy at a daily dose of 1mg/kg body weight, and increased gradually to 3mg/kg, as required. Cumulative dose of 1 to 3g of Amphotericin B as L-AmB over 3 to 4 weeks is normally recommended. Dosage must be adjusted to the specific requirement of each patient.

Mucormycosis
The recommended starting dose is 5mg/kg/day and the course duration should be determined on an individual basis and courses can be up to 6-8 weeks. Longer duration of therapy may be required for deep seated infections or in cases of prolonged courses of chemotherapy or neutropenia.

Literature data on the safety and efficacy of L-AmB at higher doses are limited. Therefore, a benefit-risk assessment should be made on an individual patient level to determine whether the potential benefits of treatment are considered to outweigh the known increased risk of toxicity at higher doses.

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

treatment of febrile neutropenia

The recommended daily dose is 3 mg/kg body weight per day. Treatment should be continued until the recorded temperature is normalised for 3 consecutive days. In any event, treatment should be discontinued after a maximum of 42 days.

Paediatric population
From literature data – L-amB has been studied in paediatric patient aged one month to 18 years old without reports of unusual adverse events. Doses used were same as in adults.

L-AmB is not recommended for use in children below 1 month old due to lack of data on safety and efficacy.

Elderly patients
No change in dose or frequency of dosing is required in elderly patients.

Renal impairment
From literature data, L-AmB has been administered to a large number of patients with pre-existing renal impairment at starting doses ranging from 1-3mg/kg/day in clinical trials and no adjustment in dose or frequency of administration was required.

Hepatic impairment
No data are available on which to make a dose recommendation for patients with hepatic impairment.

Method of administration
Instruction for use:
Reconstitute each vial of Amphonex 50 MG 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 up to 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 administration should be carried out using controlled infusion device, over a period of approximately 120 min. Infusion time may reduce to approximately 60 minutes in patients in whom the treatment is well tolerated. 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.

s

Physical and chemical stability of the reconstituted product as well diluted infusion mixture has been found satisfactory up to 48 hours when stored under refrigerated conditions (2°C - 8°C). However, it is advisable to use the infusion mixture of L-AmB immediately after dilution as Amphonex contains no preservatives.

3. Contraindications

L-AmB is contra-indicated in patients with known hypersensitivity to Amphotericin B or any of its excipients, unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to L-AmB.

4. Special warnings and precautions for use

From literature data following warnings and precautions should be taken.

Anaphylaxis and anaphylactoid reactions

Anaphylaxis and anaphylactoid reactions have been reported in association with L-AmB. Allergic type reactions, including severe infusion-related reactions can occur during administration of amphotericin-containing products, including L-AmB. Therefore, administration of test dose is still advisable before a new course of treatment. If a severe allergic or anaphylactic/ anaphylactoid reactions occurs, the infusion should be immediately discontinued, and the patient should not receive further infusion of L-AmB.

Infusion related reactions

Other severe infusion-related reactions can occur during administration of amphotericin B-containing products, including L-AmB. Although, infusion related reactions are not usually serious, consideration of precautionary measures for prevention or treatment of these reactions should be given to patients who receive L-AmB. Slower infusion rates (over 2 hours) or routine doses diphenhydramine, paracetamol, pethidine and/or hydrocortisone have been reported to be successful in the prevention or treatment of infusion related reactions.

Renal toxicity

L-AmB has been shown to be significantly less toxic than conventional Amphotericin B , particularly with respect to nephrotoxicity; however, renal adverse reactions may still occur.

In studies from literature comparing L-AmB 3 mg/kg daily with higher doses (5, 6 or 10 mg/kg daily), it was found that the incidence rates of increased serum creatinine, hypokalaemia and hypomagnesaemia were notably higher in the high dose groups.

In particular, caution should be exercised when prolonged therapy is required. Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium as well as renal, hepatic and haematopoietic function should be performed, at least once weekly. This is particularly important in patients receiving concomitant nephrotoxic medications. Renal function should be closely monitored in these patients. Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of L-AmB administration. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation.

Pulmonary toxicity

Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leukocyte transfusions. It is recommended that these infusions are separated by as long a period as possible and pulmonary function should be monitored.

In the *treatment of Diabetic Patients:*

Each vial of L-AmB 50mg contains 900mg of Sucrose. This should be taken into account when treating diabetic patients.

5. Interactions with other medicinal products and other forms of interactions

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

From literature data, following medicinal products are known to interact with amphotericin B and may interact with L-AmB:

Nephrotoxic medications

Concurrent administration of L-AmB with other nephrotoxic agents (for example ciclosporin, aminoglycosides, polymixins, tacrolimus and pentamidine) may enhance the potential for drug-induced renal toxicity in some patients. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, L-AmB was associated with significantly less nephrotoxicity compared to amphotericin B. Regular monitoring of renal function is recommended in patients receiving L-AmB with any nephrotoxic medications.

Corticosteroids, corticotropin (ACTH) and diuretics

Concurrent use of corticosteroids, ACTH and diuretics (loop and thiazide) may potentiate hypokalemia.

Digitalis glycosides

L-AmB-induced hypokalemia may potentiate digitalis toxicity.

Skeletal muscle relaxants

L-AmB-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine).

Antifungals

No evidence of benefit from the use of flucytosine with L-AmB has been observed. Whilst synergy between amphotericin and flucytosine has been reported, concurrent use may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion.

Antineoplastic agents

Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm and hypotension. Antineoplastic agents should be given concomitantly with caution.

Leukocyte transfusions

Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leukocyte transfusions. It is recommended these infusions are separated by as long a period as possible and pulmonary function should be monitored.

6. Fertility, pregnancy and lactation

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Pregnancy

The safety of L-AmB in pregnant women has not been established.

Systemic fungal infections have been successfully treated in pregnant women with conventional amphotericin B without obvious effect on the fetus, but the number of cases reported is insufficient to draw any conclusions on the safety of L-AmB in pregnancy.

L-AmB should only be used during pregnancy if the possible benefits to be derived outweigh the potential risks to the mother and fetus.

Breast-feeding

It is unknown whether L-AmB is excreted in human breast milk. A decision on whether to breastfeed while receiving L-AmB should take into account the potential risk to the child as well as the benefit of breast feeding for the child and the benefit of L-AmB therapy for the mother.

7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Some of the undesirable effects of L-AmB presented below may impact the ability to drive and use machines.

8. Undesirable effects

From literature data following adverse events were noted

[Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Very rare (<1/10,000), Not known (cannot be estimated from the available data)]

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Not known: anaemia

Immune system disorders

Uncommon: anaphylactoid reaction

Not known: anaphylactic reactions, hypersensitivity

Metabolism and nutrition disorders

Very common: hypokalaemia

Common: hyponatremia, hypocalcaemia, hypomagnesaemia, hyperglycemia,

Nervous system disorders *Common*: headache *Uncommon*: convulsion **Cardiac disorders** *Common*: tachycardia

Not known: cardiac arrest, arrhythmia

Vascular disorders

Common: hypotension, vasodilatation, flushing **Respiratory, thoracic and mediastinal disorders** *Common*: dyspnoea

Uncommon: bronchospasm **Gastrointestinal disorders** *Very common:* nausea, vomiting

Common: diarrhoea, abdominal pain

Hepatobiliary disorders

Common: abnormal liver function tests, hyper-bilirubinaemia, increased alkaline phosphatase

Skin and subcutaneous disorders

Common: rash

Not known: angioneurotic oedema Musculoskeletal and connective tissue disorders Common: back pain

Not Known: rhabdomyolysis (associated with hypokalaemia), musculoskeletal pain (described as arthralgia or bone pain)

Renal and urinary disorders

Common: increased creatinine, increased blood urea Not known: renal failure, renal insufficiency General disorders and administration site conditions Very Common: rigors, pyrexia,

Common: chest pain

Description of selected adverse reactions

Infusion-related reactions

Fever and chills/rigors are the most frequent infusion-related reactions expected to occur during L-AmB administration. Less frequent infusion-related reactions may consist of one or more of the

following symptoms: chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, hypotension and musculoskeletal pain (described as arthralgia, back pain, or bone pain). These resolve rapidly on stopping the infusion and may not occur with every subsequent dose or when slower infusion rates (over 2 hours) are used. In addition, infusion-related reactions may also be prevented by the use of premedication. However, severe infusion-related reactions may necessitate the permanent discontinuation of L-AmB.

In two double-blind, comparative literature studies, L- AmB treated patients experienced a significantly lower incidence of infusion-related reactions, as compared to patients treated with conventional amphotericin B or amphotericin B lipid complex.

In pooled study data from randomised, controlled clinical trials from literature comparing AmB L-with conventional amphotericin B therapy in greater than 1,000 patients, reported adverse reactions were considerably less severe and less frequent in L-AmB treated patients as compared with conventional amphotericin B treated patients.

Renal toxicity

Nephrotoxicity occurs to some degree with conventional amphotericin B in most patients receiving the product intravenously. In a double-blind study from literature involving 687 patients, the incidence of nephrotoxicity with L-AmB (as measured by serum creatinine increase greater than 2.0 times baseline measurement), was approximately half that for conventional amphotericin B. In another double-blind study from literature involving 244 patients, the incidence of nephrotoxicity with L-AmB (as measured by serum creatinine increase greater than 2.0 times baseline measurement) was approximately half that for Amphotericin B lipid complex.

Interference with Phosphorus Chemistry Assay

False elevations of serum phosphate may occur when samples from patients receiving L-AmB are analyzed using the PHOSm assay (e.g. used in Beckman Coulter analyzers including the Synchron LX20). This assay is intended for the quantitative determination of inorganic phosphorus in human serum, plasma or urine samples.

9. Overdose

Toxicity of L-AmB due to acute overdose has not been defined. If overdose should occur, cease administration immediately. Carefully monitor clinical status including renal and hepatic function, serum electrolytes and haematological status. Haemodialysis or peritoneal dialysis does not appear to affect the elimination of L-AmB.

Special populations (including paediatric population):

No additional information is available in special populations.

5. Pharmacological properties

1. Pharmacodynamic properties ATC classification

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

Mechanism of action and pharmacodynamic effects

Amphotericin B is a macrocyclic, polyene antifungal antibiotic produced by Streptomyces nodosus. Amphotericin B is fungistatic or fungicidal depending on the concentration attained in body fluids and the susceptibility of the fungus. The molecule is thought to act by binding to sterols in the fungal cell membrane, with a resulting change in membrane permeability, allowing leakage of a variety of small molecules. Mammalian cell membranes also contain sterols, and it has been suggested that the damage to human cells and fungal cells caused by amphotericin B may share common mechanisms. The lipophilic moiety of amphotericin allows the molecule to be integrated into the lipid bilayer of the liposomes. Liposomes are closed, spherical vesicles formed from a variety of amphiphilic substances such as liposomes. Liposomes are closed, spherical vesicles formed from a variety of amphiphilic substances such as phospholipids. Phospholipids arrange themselves into membrane bilayers when exposed to aqueous solutions.

Clinical efficacy and safety

The efficacy of L-AmB has been established in a number of clinical trials for the treatment of systemic mycotic infections, as empirical therapy for fever of unknown origin in neutropenic patients and for the treatment of visceral leishmaniasis. These studies include comparative randomized studies of L-AmB versus conventional amphotericin B in confirmed Aspergillus and Candida infections where the efficacy of both medicinal products was equivalent. In both adult and paediatric febrile neutropenic patients presumed to have fungal infection, the results of a randomized, double-blind, clinical trial demonstrated that L-AmB administered at 3 mg/kg/day is as effective as conventional amphotericin B. The efficacy of L-AmB in the treatment of visceral leishmaniasis has been clearly demonstrated in a large population of immunocompetent and immunocompromised patients.

Invasive Filamentous Fungal Infections (IFFI) including Aspergillus spp.

The efficacy of L-AmB has been demonstrated in a prospective, randomised, multicentre study as first line treatment in immunocompromised, mainly neutropenic adults and children (> 30 days old) with proven or probable IFFIs (AmBiLoad Study).

Patients were monitored for 12 weeks. A standard-dose regimen of 3 mg/kg/day (N=107) was compared to a loading dose regimen of 10 mg/kg/day (N=94) for the first 14 days of treatment. The favourable overall response rates were 50% of subjects in the standard-dose group and 46% of the subjects in the loading-dose group in the modified intent-to-treat analysis set. Differences were not statistically significant. The median time to resolution of fever was similar in the standard-dose and loading-dose groups (6 and 5 days, respectively). Twelve weeks after the first dose of L-AmB, survival was 72% in the standard-dose group and 59% in the loading-dose group, a difference that was not statistically significant.

Invasive candidiasis

L-AmB (3 mg/kg/day) was as effective as Micafungin (100 mg/day [Body weight > 40 kg] or 2 mg/kg/day [Body weight ≤ 40 kg]) as first line treatment of candidaemia and invasive candidiasis in a randomised, double-blind, multinational non-inferiority study in adults and children. L-AmB and Micafungin were administered for a median duration of 15 days. The favourable overall response was 89.5% (170/190) in the L-AmB group and 89.6% (181/202) in the Micafungin group (per protocol analysis set). The paediatric sub-study, which enrolled 98 patients of whom 57 were

<2 years old, (including 19 premature infants), showed favourable overall response rates of: 88.1% (37/42) for L-AmB and 85.4% (35/41) for Micafungin (per protocol analysis set).

Invasive mucormycosis (zygomycosis)

There are no large-scale randomised clinical trials in mucormycosis. The working group in zygomycosis of the European confederation of medical mycology (ECMM) prospectively collected cases of patients with zygomycosis, 130 patients received L-AMB as first-line therapy, either alone (68) or in combination. In patients who received it as the only antifungal medication, the survival rate was 68%. In patients that were cured, the median duration of treatment was 55 days (range 14-169 days) and the median daily dose was 5 mg/kg (range 3-10 mg/kg), (Skiada et al; Clin Microbiol Infect 2011;17 (12):1859-67).

In a prospective pilot study of high-dose (10 mg/kg/day) L-AmB for the initial treatment of mucormycosis, 29 patients receiving 10 mg/kg/day had a median treatment duration of 13.5 days (range 0-28 days). The primary endpoint was treatment success at week 4 or at end of treatment (if earlier) and 12 (36%) out of 33 evaluable patients responded, including 18% with complete response; the response rate increased to 45% at week 12. The survival rate was 62% at week 12 and 47% at week 24 (Lanternier et al; J Antimicrob Chemother 2015; 70(11):3116-23).

Paediatric population

The pharmacodynamic profile of L-AmB in paediatric patients is consistent with that described in adult patients.

2. Pharmacokinetic properties

Following pharmacokinetic properties is from literature data-

The pharmacokinetic profile of L-AmB, based upon total plasma concentrations of amphotericin B, was determined in cancer patients with febrile neutropenia and bone marrow transplant patients who received 1-hour infusions of 1.0 to 7.5mg/kg/day L-AmB for 3 to 20 days. L-AmB has a significantly different pharmacokinetic profile from that reported in the literature for conventional presentations of amphotericin B, with higher amphotericin B plasma concentrations (C_{max}) and increased exposure (AUC0-24) compared to conventional amphotericin B. After the first dose and last dose, the pharmacokinetic parameters of amphotericin B (mean ± standard deviation) ranged from:

C_{max}	7.3 µg/ml (± 3.8) to 83.7 µg/ml (± 43.0)
$T_{1/2}$	6.3 hr (± 2.0) to 10.7 hr (± 6.4)
AUC_{0-24}	27 µg.hr/ml (±14) to 555 µg.hr/ml (± 311)
Clearance (Cl)	11 ml/hr/kg (± 6) to 51 ml/hr/kg (± 44)
Volume of distribution (Vss)	0.10 L/kg (± 0.07) to 0.44 L/kg (±0.27)

Minimum and maximum pharmacokinetic values do not necessarily relate to the lowest and highest doses, respectively.

Following administration of L-AmB steady state was reached quickly (generally within 4 days of dosing).

Absorption

Amphotericin B pharmacokinetics following the first dose of L-AmB appear non-linear such that amphotericin B concentrations are greater than proportional with increasing dose. This non-proportional dose response is believed to be due to saturation of reticuloendothelial L-AmB clearance. There was no significant drug accumulation in the plasma following repeated administration of 1 to 7.5mg/kg/day.

Distribution

Volume of distribution on day 1 and at steady state suggests that there is extensive tissue distribution of amphotericin B.

Elimination

After repeated administration of L-AmB, the terminal elimination half-life (t½β) of amphotericin B was approximately 7 hours. The excretion of L-AmB has not been studied. The metabolic pathways of amphotericin B and L-AmB are not known. Due to the size of the liposomes, there is no glomerular filtration and renal elimination of L-AmB, thus avoiding interaction of amphotericin B with the cells of the distal tubuli and reducing the potential for nephrotoxicity seen with conventional amphotericin B presentations.

Special populations Renal Impairment

The effect of renal impairment on the pharmacokinetics of L-AmB has not been formally studied. Data suggest that no dose adjustment is required in patients undergoing haemodialysis or filtration procedures, however, L-AmB administration should be avoided during the procedure.

Pharmacokinetic/pharmacodynamics relationship

Mechanism of resistance

Intrinsic resistance, though rare, may be primarily due to decrease in ergosterol or a change in the target lipid, leading to reduced binding of amphotericin B to the cell membrane.

Breakpoints

EUCAST breakpoints for L-AmB have not yet been established, however, susceptibility to L-AmB may differ to that of amphotericin B deoxycholate.

Amphotericin B, the antifungal component of L-AmB, is active in vitro against many species of fungi, most strains of Histoplasma capsulatum, Coccidioides immitis, Candida spp, Blastomyces dermatidis, Rhodotorula, Cryptococcus, neoformans, Sporothrix schenkii and Aspergillus fumigatus, Penicillium marneffi, and members of the mucormycetes group of moulds including Mucor mucedo, Rhizomucor and Rhizopus oryzae.

The majority of clinically important fungal species seem to be susceptible to amphotericin B, although intrinsic resistance has rarely been reported, for example, for some strains of S. schenckii,
C. glabrata, C.krusei, C. tropicalis, C. lusitaniae, C. parapsilosis and Aspergillus terreus.

L-AmB has been shown to be effective in animal models of visceral leishmaniasis (caused by Leishmania infantum and Leishmania donovani).

3. Preclinical safety data

Acute toxicity studies in rodents showed that L-AmB was 50-fold to 80-fold less toxic than conventional formulation of Amphotericin B deoxycholate.

From literature studies, in sub-chronic 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. No adverse effects on male or female reproductive function were noted in rats.

6. Pharmaceutical particulars

6.1. List of excipients

- Hydrogenated soy phosphatidyl choline IH
- Cholesterol Ph. Eur.
- Di-stearoyl phosphatidylglycerol IH
- Alpha tocopherol Ph. Eur.
- Sucrose Ph. Eur
- Disodium succinate hexahydrate
- Hydrochloric acid
- Water for injection Ph. Eur

6.2. Incompatibilities

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. 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 L-AmB.

6.3. Shelf life

36 months.

Shelf –life of Amphonex after first opening

In-use storage times and conditions prior to administration are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Shelf-life after reconstitution**:**

Glass vials for 24 hours at 25±2°C exposed to ambient light

Glass vials and polypropylene syringes up to 7 days at 2-8°C

Do not store above 30^0C. Do not freeze. Keep the container in the outer carton.

6.4. Special precautions for storage

Do not store above 30^0C. Do not freeze. Keep the container in the outer carton.

6.5. Nature and contents of container

Single dose vials containing 50mg Amphotericin B. Each vial is packed individually in a carton with 5µ syringe filter and a package insert.

20 ml Clear, colourless, USPType1 (Neutral Borosilicate) Tubular Vial with Rubber bung 20 mm with 20 mm Aluminium Flip Off seal

6.6.**Special precautions for disposal and other handling**

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

7. **Marketing authorization holder**

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

8. Marketing authorization number

TAN 21 HM 0376

9. **Date of first authorization date**
2021-10-09

10. **Date of revision of the text**