SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amphotericin B SUN Pharma liposomal 50 mg powder for dispersion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

After reconstitution, the concentrate contains 4 mg/ml amphotericin B.

Excipients with known effect:

Each vial contains 213 mg of hydrogenated soy phosphatidylcholine and 900 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for dispersion for infusion.

Sterile yellow to dark yellow lyophilised cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amphotericin B SUN Pharma liposomal 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 with Amphotericin B SUN Pharma liposomal include: disseminated candidiasis, aspergillosis, mucormycosis, chronic mycetoma, cryptococcal meningitis and visceral leishmaniasis.

Amphotericin B SUN Pharma liposomal should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.

4.2 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 Amphotericin B SUN Pharma liposomal is administered at a dose recommended for amphotericin B deoxycholate.

Posology
Anaphylaxis and anaphylactoid reactions can occur at any point of treatment of Amphotericin B SUN Pharma liposomal therefore the patient should be monitored closely during every treatment of Amphotericin B SUN Pharma liposomal (see section 4.4).

Treatment of mycoses
Therapy is usually instituted at a daily dose of 3 to 5 mg/kg of body weight for a minimum of 14 days. Dosage of amphotericin B as Amphotericin B SUN Pharma liposomal must be adjusted to the specific requirements of each patient.

Mucormycosis
For suspected or confirmed infection, the recommended starting dose is 5 to 10 mg/kg/day.
In patients with brain involvement or solid-organ transplant, dose at 10 mg/kg/day.
Avoid slow escalation of doses. The duration of therapy should be determined on an individual basis. Courses of up to 6 – 8 weeks are commonly used in clinical practice; longer durations of therapy may be required for deep seated infections or in cases of prolonged courses of chemotherapy or neutropenia.
Although doses greater than 5 mg/kg and up to a maximum of 10 mg/kg have been used in clinical trials and clinical practice, data on the safety and efficacy of Amphotericin B SUN Pharma liposomal for the treatment of mucormycosis at these 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 Amphotericin B SUN Pharma liposomal doses (see section 4.4).

HIV associated Cryptococcal meningitis
Administer a single dose of 10 mg/kg Amphotericin B SUN Pharma liposomal on day 1, in combination with daily flucytosine 100 mg/kg and daily fluconazole 1200 mg, both administered for 14 days.
After the 2-week induction period, patients should receive fluconazole 800 mg daily for 8 weeks and then at a dose of 200 mg daily thereafter at the treating physician's discretion.

Treatment of visceral leishmaniasis
A total dose of 21.0 - 30.0 mg/kg of body weight given over 10-21 days may be used in the treatment of visceral leishmaniasis. Particulars as to the optimal dosage and the eventual development of resistance are as yet incomplete. The product should be administered under strict medical supervision.

Empirical treatment of febrile neutropenia

The recommended daily dose is 3 to 5 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
Both systemic fungal infections in children and presumed fungal infections in children with febrile neutropenia have been successfully treated with Amphotericin B SUN Pharma liposomal, without reports of unusual adverse events. Amphotericin B SUN Pharma liposomal has been studied in paediatric patients aged one month to 18 years old. Doses used in these clinical studies were the same as those used in adults on a mg/kg body weight basis.
Amphotericin B SUN Pharma liposomal is not recommended for use in children below 1 month old due to lack of data on safety and efficacy.

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

Renal impairment
Amphotericin B SUN Pharma liposomal has been administered to a large number of patients with pre-existing renal impairment at starting doses ranging from 1-3 mg/kg/day in clinical trials and no adjustment in dose or frequency of administration was required (See section 4.4).

Hepatic impairment
No data are available on which to make a dose recommendation for patients with hepatic impairment (See section 4.4).

Method of administration
Amphotericin B SUN Pharma liposomal should be administered by intravenous infusion over a 30 - 60 minute period and the patient closely observed. For doses greater than 5mg/kg/day, intravenous infusion over a 2 hour period is recommended (see section 4.4). The recommended concentration for intravenous infusion is 0.20 mg/ml to 2.00 mg/ml amphotericin B as Amphotericin B SUN Pharma liposomal.

For instructions on reconstitution and dilution of the product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to Amphotericin B SUN Pharma liposomal therapy.

4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions
Anaphylaxis and anaphylactoid reactions have been reported in association with Amphotericin B SUN Pharma liposomal infusion. Allergic type reactions, including severe infusion-related reactions can occur during administration of amphotericin-containing products, including Amphotericin B SUN Pharma liposomal (see section 4.8). Therefore, every dose of Amphotericin B SUN Pharma liposomal should be infused over 30-60 minutes and the patient closely monitored every time. If a severe

allergic or anaphylactic/anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of Amphotericin B SUN Pharma liposomal.

Infusion-related reactions
Other severe infusion-related reactions can occur during administration of amphotericin B-containing products, including Amphotericin B SUN Pharma liposomal (see section 4.8). Although infusion-related reactions are not usually serious, consideration of precautionary measures for the prevention or treatment of these reactions should be given to patients who receive Amphotericin B SUN Pharma liposomal therapy. Slower infusion rates (over 2 hours) or routine doses of diphenhydramine, paracetamol, pethidine and/or hydrocortisone have been reported as successful in their prevention or treatment.

Renal toxicity
Amphotericin B SUN Pharma liposomal has been shown to be substantially less toxic than conventional amphotericin B, particularly with respect to nephrotoxicity; however, renal adverse reactions may still occur.
In studies comparing Amphotericin B SUN Pharma liposomal 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. 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 Amphotericin B SUN Pharma liposomal 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. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Most of them occurred in patients with renal impairment, and some cases after potassium supplementation in patients with previous hypokalaemia. Therefore, renal function and laboratory evaluation of potassium, should be measured before and during treatment. This is particularly important in patients with pre-existing renal disease, who have already experienced renal failure, or in patients receiving concomitant nephrotoxic medications (see section 4.5).

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.

Diabetic patients
Amphotericin B SUN Pharma liposomal contains approximately 900 mg of sucrose in each vial. This should be taken into account when treating diabetic patients.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per 50 mg vial, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with Amphotericin B SUN Pharma liposomal. However, the following medicinal products are known to interact with amphotericin B and may interact with Amphotericin B SUN Pharma liposomal:

Nephrotoxic medications
Concurrent administration of Amphotericin B SUN Pharma liposomal 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, Amphotericin B SUN liposomal Pharma was associated with significantly less nephrotoxicity compared to amphotericin B. Regular monitoring of renal function is recommended in patients receiving Amphotericin B SUN Pharma liposomal with any nephrotoxic medications.

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

Digitalis glycosides
Amphotericin B SUN Pharma liposomal-induced hypokalemia may potentiate digitalis toxicity.

Skeletal muscle relaxants
Amphotericin B SUN Pharma liposomal-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine).

Antifungals
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, therefore a benefit:risk assessment should be made on an individual patient level.

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.

4.6 Fertility, pregnancy and lactation

Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Pregnancy
The safety of Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal in pregnancy.

Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal is excreted in human breast milk. A decision on whether to breastfeed while receiving Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal therapy for the mother.

4.7 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 Amphotericin B SUN Pharma liposomal presented below may impact the ability to drive and use machines.

4.8 Undesirable effects

Summary of adverse reactions

The following adverse reactions have been attributed to Amphotericin B SUN Pharma liposomal based on clinical trial data and post-marketing experience. The frequency is based on analysis from pooled clinical trials of 688 Amphotericin B SUN Pharma liposomal treated patients; the frequency of adverse reactions identified from post-marketing experience is not known. Adverse reactions are listed below by body system organ class using MedDRA and are sorted by frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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, hyperkalaemia

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, hyperbilirubinaemia, 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 Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal (see section 4.4).

In two double-blind, comparative studies, Amphotericin B SUN Pharma liposomal 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 comparing Amphotericin B SUN Pharma liposomal with conventional amphotericin B therapy in greater than 1,000 patients, reported adverse reactions were considerably less severe and less frequent in Amphotericin B SUN Pharma liposomal treated patients as compared with conventional amphotericin B treated patients.

A randomized phase III study assessed a single 10 mg/kg dose of Amphotericin B SUN Pharma liposomal with a backbone of 14 days flucytosine and fluconazole, compared to the control group (1-week conventional amphotericin B plus flucytosine followed by 1 week of fluconazole) in the treatment of HIV associated cryptococcal meningitis. The Amphotericin B SUN Pharma liposomal treated patients experienced fewer grade 3 or 4 adverse events compared to the control group. The safety profile observed in this patient population was consistent with the overall safety profile for Amphotericin B SUN Pharma liposomal.

Renal toxicity

Nephrotoxicity occurs to some degree with conventional amphotericin B in most patients receiving the product intravenously. In a double-blind study involving 687 patients, the incidence of nephrotoxicity with Amphotericin B SUN Pharma liposomal (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 involving 244 patients, the incidence of nephrotoxicity with Amphotericin B SUN Pharma liposomal (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 Amphotericin B SUN Pharma liposomal 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The toxicity of Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal.

Special populations (including paediatric population):
No additional information is available in special populations.

5.1 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 phospholipids. Phospholipids arrange themselves into membrane bilayers when exposed to aqueous solutions.

Clinical efficacy and safety

The efficacy of Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal administered at 3 mg/kg/day is as effective as conventional amphotericin B. The efficacy of Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal 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 IFFls (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 Amphotericin B SUN Pharma liposomal, survival was 72% in the standard-dose group and 59% in the loading-dose group, a difference that was not statistically significant.

Invasive candidiasis

Amphotericin B SUN Pharma liposomal (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. Amphotericin B SUN Pharma liposomal and Micafungin were administered for a median duration of 15 days. The favourable overall response was 89.5% (170/190) in the Amphotericin B SUN Pharma liposomal 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 Amphotericin B SUN Pharma liposomal 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 liposomal amphotericin B (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) liposomal amphotericin B 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).

Cryptococcal meningitis

A randomized phase III study assessed a single 10 mg/kg dose of Amphotericin B SUN Pharma liposomal with a backbone of 14 days flucytosine and fluconazole, compared to the control group (1-week conventional amphotericin B plus flucytosine followed by 1 week of fluconazole) in the treatment of HIV associated cryptococcal meningitis. Patients were randomized (1:1) to receive either a single dose (10 mg/kg) of Amphotericin B SUN Pharma liposomal plus 14 days of flucytosine (100 mg/kilogram/day) and fluconazole (1200 mg/day) or amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg/kg/day) for 7 days, followed by fluconazole (1200 mg/day) on days 8 through 14. After the 2-week induction period, all patients received fluconazole at a dose of 800 mg per day for 8 weeks and then at a dose of 200 mg per day thereafter. Antiretroviral therapy was initiated, reinitiated, or switched to a new antiretroviral therapy with a different agent during weeks 4 to 6 and was chosen in accordance with national guidelines.

The primary endpoint was death from any cause at 10 weeks after randomization.

The study concluded that single-dose liposomal amphotericin B combined with flucytosine and fluconazole was noninferior to the WHO-recommended treatment for HIV-associated cryptococcal meningitis and was associated with fewer adverse events.

Paediatric population

The pharmacodynamic profile of Amphotericin B SUN Pharma liposomal in paediatric patients is consistent with that described in adult patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of Amphotericin B SUN Pharma liposomal (liposomal amphotericin B (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 1hour 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 (AUC_{0-24}) 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 ½	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 (V_{ss})	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 liposomal amphotericin B (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 ($t½_{\beta}$) of amphotericin B was approximately 7 hours. The excretion of L-AmB has not been studied

Metabolism
. 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).

5.3 Preclinical safety data

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.

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

Hydrogenated soy phosphatidylcholine

Distearoylphosphatidylglycerol sodium

Cholesterol

Alpha tocopherol

Sucrose

Disodium succinate hexahydrate

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Liposomal amphotericin B is incompatible with saline solutions and may not be mixed with other medicinal products or electrolytes.

6.3 Shelf life

Amphotericin B SUN Pharma liposomal 50 mg powder for dispersion for infusion:

2 years

Shelf - life of Amphotericin B SUN Pharma liposomal after first opening

Amphotericin B SUN Pharma liposomal 50 mg powder for dispersion for infusion does not contain any preservative. Therefore, from a microbiological point of view, once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution and dilution has taken place under controlled and validated aseptic conditions.

However, the following chemical and physical in-use stability data for Amphotericin B liposomal has been demonstrated:

Shelf-life after reconstitution:

Store reconstituted solution with Sterile Water for Injection at 25±2°C exposed to ambient light in Glass vial for 24 hours.

Store reconstituted solution with Sterile Water for Injection at 2-8°C in Glass Vial for 48 hours.

Store reconstituted solution with Sterile Water for Injection at 2-8°C in polypropylene syringes up to 48 hours.

Do not freeze.

DO NOT STORE partially used vials for future patient use.

Shelf-life after dilution with dextrose:

Admixture solution of Amphotericin B Liposome for Injection, 50 mg/vial with 5% Dextrose Injection at 2 mg/ml and 0.2 mg/ml concentration in PVC infusion bag is found stable upto 6 hours at temperature 25±2°C.

Do not freeze.

See table below for recommendations.

Diluent	**Concentration of Amphotericin B mg/ml**	**Recommended duration of storage at 25±2°C**
5% Dextrose injection	2.0	6 hours
	0.2	6 hours

6.4 Special precautions for storage

Amphotericin B SUN Pharma liposomal unopened vials:

This product does not require any special storage condition.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amphotericin B SUN Pharma liposomal is packed in 20 ml Type I clear glass vials with a grey butyl rubber stopper and a golden flip-off seal.

Amphotericin B SUN Pharma liposomal is supplied in packs of 1 vial or 10 vials together with 1 or 10 filters, respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

READ THIS ENTIRE SECTION CAREFULLY BEFORE BEGINNING RECONSTITUTION.

Amphotericin B SUN Pharma liposomal is not interchangeable with other amphotericin products.

Amphotericin B SUN Pharma 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 SUN Pharma 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 SUN Pharma liposomal should be administered through a separate line.

Do NOT mix Amphotericin B SUN Pharma 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 SUN Pharma liposomal, or in the materials specified for reconstitution and dilution.

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

1. Add 12 ml of Sterile Water for Injection to each Amphotericin B SUN Pharma liposomal vial, to yield a preparation containing 4 mg/ml amphotericin.
2. IMMEDIATELY after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 seconds to completely disperse the Amphotericin B SUN Pharma 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 SUN Pharma liposomal to be further diluted (see table below).
4. The infusion solution is obtained by dilution of the reconstituted Amphotericin B SUN Pharma 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 as Amphotericin B SUN Pharma liposomal (see table below).
5. Withdraw the calculated volume of reconstituted Amphotericin B SUN Pharma liposomal into a sterile syringe. Using the 5 micron filter provided, instill the Amphotericin B SUN Pharma 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.

Preparation of Amphotericin B SUN Pharma liposomal for Infusion

An example is provided in the table below of the preparation of Amphotericin B SUN liposomal dispersion for infusion at a dose of **3mg/kg/day** in dextrose 5% solution for infusion. Note that this table relates to doses of **3mg/kg/day** only, however other

doses than this may be prescribed for a patient. If a dose other than **3mg/kg/day** has been prescribed for a patient, then the appropriate calculations must be undertaken and the table cannot be used.

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

Weight (kg)	Number of vials	Amount Amphotericin B SUN Pharma liposomal (mg) to be withdrawn for further dilution	Volume of reconstituted Amphotericin B SUN Pharma 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 SUN Pharma liposomal plus 5% dextrose)	Volume of 5% dextrose needed (ml)	Total volume (ml; Amphotericin B SUN Pharma 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 SUN Pharma liposomal (50mg) is reconstituted with 12ml Water for Injection to provide a concentration of 4 mg/ml amphotericin B.

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

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.

Polarisavenue 87

2132 JH Hoofddorp

The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

22/08/2025