SUMMARY OF PRODUCT CHARACTERISTICS

AmBisome®

1. NAME OF THE MEDICINAL PRODUCT

AmBisome Liposomal Amphotericin B 50mg Powder for concentrate for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of amphotericin B (50,000 units) encapsulated in liposomes
After reconstitution, the concentrate contains 4 mg/mL amphotericin B.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Liposomal Amphotericin B 50mg Powder for concentrate for infusion.
A sterile, yellow lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AmBisome is indicated:
In the treatment of severe systemic and/or deep mycoses where toxicity (particularly nephrotoxicity) precludes the use of conventional systemic amphotericin B in effective dosages.

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

In the treatment of systemic fungal infections in immuno-compromised patients (e.g. patients with AIDS or Cancer).

As the primary therapy of visceral leishmaniasis in immunocompetent patients and immunocompromised patients (e.g. HIV Positive).

In the empirical treatment of presumed fungal infection in febrile neutropenic patients.

4.2 Posology and method of administration

AmBisome should be administered by intravenous infusion over a 30 - 60 minute period. For doses greater than 5 mg/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 AmBisome.

Treatment of systemic mycoses and visceral leishmaniasis
Therapy is usually instituted at a daily dose of 1.0 mg/kg of body weight, and increased stepwise to 3.0 mg/kg, as required. Dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient. A cumulative dose 1.0 – 3.0 g of AmBisome over 3-4 weeks has been typical of the treatment necessary for the resolution of mycoses.

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 Patients: Systemic fungal infections and visceral leishmaniasis in children1, 2 and presumed fungal infections in children with febrile neutropenia have been successfully treated with AmBisome without reports of unusual adverse events. AmBisome has been studied in paediatric patients aged one month to 18 years old. Dosage should be calculated on the same per-Kg body weight basis as for adults.

The safety and efficacy of AmBisome has not been established in infants under one month old.

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

Renal Impairment: AmBisome has been administered to patients with pre-existing renal impairment at doses of 1-5 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 Warnings and Precautions for Use (See section 4.4).

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

4.3 Contraindications
AmBisome is contraindicated in those patients who have shown hypersensitivity to any of its constituents unless, in the opinion of the physician, the condition requiring treatment is life threatening and amenable only to AmBisome therapy.

4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions have been reported in association with AmBisome infusion. If a severe anaphylactic/anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of AmBisome.

Other severe infusion-related reactions can occur during administration of amphotericin B-containing products, including AmBisome (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 AmBisome therapy. Slower infusion rates (over 2 hours) or routine doses of diphenhydramine, paracetamol, pethidine, and/or hydrocortisone have been reported as successful in its prevention or treatment.

AmBisome has been shown to be substantially less toxic than conventional amphotericin B particularly with respect to nephrotoxicity; however, adverse reactions including renal adverse reactions may still occur.

In studies comparing AmBisome 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, hypokalemia and hypomagnesaemia were notably higher in the high dose groups.

Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium, as well as renal, hepatic and haematopoietic function should be performed. This is particularly important in patients receiving concomitant nephrotoxic medications (see section 4.5). Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of AmBisome 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.

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.

In the Treatment of Diabetic Patients: It should be noted that AmBisome contains approximately 900 mg of sucrose in each vial.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with AmBisome. However, the following drugs are known to interact with amphotericin B and may interact with AmBisome:

Nephrotoxic medications: Concurrent administration of amphotericin B with other nephrotoxic agents (for example, ciclosporin, aminoglycosides and pentamidine) may enhance the potential for drug-induced renal toxicity in some patients. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, AmBisome was associated with significantly less nephrotoxicity compared to amphotericin B.

Regular monitoring of renal function is recommended in patients receiving AmBisome with any nephrotoxic medications.

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

Digitalis glycosides: AmBisome-induced hypokalemia may potentiate digitalis toxicity.

Skeletal muscle relaxants: AmBisome-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine).

Antifungals: Concurrent use with flucytosine 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.

4.6 Pregnancy and lactation

Pregnancy

Teratogenicity studies in both rats and rabbits have concluded that AmBisome had no teratogenic potential in these species.

The safety of AmBisome in pregnant women has not been established. AmBisome should only be used during pregnancy if the possible benefits to be derived outweigh the potential risks to the mother and foetus.

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

Lactation:
It is unknown if AmBisome is excreted in human milk.
A decision on whether to breastfeed while receiving AmBisome should take into account the potential risk to the child as well as the benefits of breast feeding for the child and the benefit of AmBisome 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 AmBisome presented below may impact the ability to drive and use machines.

4.8 Undesirable effects

Fever and chills/rigors are the most frequent infusion-related reactions expected to occur during AmBisome 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 resolved 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 AmBisome (see section 4.4).

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

Nephrotoxicity occurs to some degree with conventional amphotericin B, in most patients receiving the drug intravenously. In two, double-blind studies, the incidence of nephrotoxicity with AmBisome (as measured by serum creatinine increase greater than 2.0 times baseline measurement), is approximately half of that reported for conventional amphotericin B or amphotericin B lipid complex.

The following adverse reactions have been attributed to AmBisome, based on clinical trial data and post-marketing experience. The frequency is based on analysis from pooled clinical trials of 688 AmBisome treated patients; the frequency of adverse events 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)
Rare	(≥ 1/10,000 to <1/1,000)
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: hypokalemia
Common: hyponatraemia, hypocalcaemia, hypomagnesaemia, hyperglycaemia
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: liver function tests abnormal, hyperbilirubinaemia, alkaline phosphatase increased

SKIN AND SUBCUTANEOUS DISORDERS
Common: rash
Not known: angioneurotic oedema

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Common: back pain
Not Known: rhabdomyolysis (associated with hypokalemia), musculoskeletal pain (described as arthralgia or bone pain)

RENAL AND URINARY DISORDERS
Common: increased creatinine, blood urea increased
Not known: renal failure, renal insufficiency

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Very Common: rigors, pyrexia
Common: chest pain

Interference with Phosphorus Chemistry Assays:
False elevations of serum phosphate may occur when samples from patients receiving AmBisome 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il
Or by email to DrugSafety.Israel@gilead.com

4.9 Overdose
The toxicity of AmBisome 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 haematologic status. Haemodialysis or peritoneal dialysis does not appear to affect the elimination of AmBisome.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, antibiotics. ATC code: J02AA01
Amphotericin B is a macrocyclic, polyene antifungal antibiotic produced by Streptomyces nodosus.

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. The lipophilic moiety of amphotericin B allows the drug to be integrated into the lipid bilayer of the liposomes.

Amphotericin B is fungistatic or fungicidal depending on the concentration attained in body fluids and the susceptibility of the fungus. The drug probably acts by binding to sterols in the fungal cell membrane, with a resultant 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.

Microbiology: Amphotericin B, the antifungal component of AmBisome, shows a high order of in vitro activity against many species of fungi. Most strains of *Histoplasma capsulatum, Coccidioides immitis, Candida sp., Blastomyces dermatitidis, Rhodotorula, Cryptococcus neoformans, Sporothrix schenckii, Mucor mucedo* and *Aspergillus fumigatus*, are inhibited by concentrations of amphotericin B ranging from 0.03 to 1.0 mcg/ml in vitro. Amphotericin B has minimal or no effect on bacteria and viruses.

AmBisome has been shown to be effective in animal models of visceral leishmaniasis (caused by *Leishmania infantum* and *Leishmania donovani*). In mice infected with *Leishmania infantum* and treated with AmBisome 3 mg/kg for 3-7 doses, all dosage regimens of AmBisome cured mice more promptly than sodium stibogluconate, and no toxicity was seen. In mice infected with *Leishmania donovani*, AmBisome was >5 times more effective and >25 times less toxic than amphotericin B.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of AmBisome, 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 AmBisome for 3 to 20 days. AmBisome 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}) following

administration of AmBisome than conventional amphotericin B. After the first and last dose the pharmacokinetic parameters of AmBisome (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 555μg.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 come from the lowest and highest doses, respectively. Following administration of AmBisome steady state was reached quickly (generally within 4 days of dosing). AmBisome pharmacokinetics following the first dose appear non-linear such that serum AmBisome concentrations are greater than proportional with increasing dose. This non-proportional dose response is believed to be due to saturation of reticuloendothelial AmBisome clearance. There was no significant drug accumulation in the plasma following repeated administration of 1 to 7.5mg/kg/day. Volume of distribution on day 1 and at steady state suggests that there is extensive tissue distribution of AmBisome. After repeated administration of AmBisome the terminal elimination half-life ($t_{½\beta}$) for AmBisome was approximately 7 hours. The excretion of AmBisome has not been studied. The metabolic pathways of amphotericin B and AmBisome are not known. Due to the size of the liposomes there is no glomerular filtration and renal elimination of AmBisome, 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.

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

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 AmBisome toxicity were the liver and kidneys, both known target organs for amphotericin B toxicity.

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

Carcinogenicity studies have not been conducted with AmBisome.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hydrogenated soy phosphatidylcholine.
Cholesterol
Distearoylphosphatidylglycerol
Alpha-tocopherol.
Sucrose
Disodium succinate hexahydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

AmBisome is not physically compatible with saline solutions and should not be mixed with other drugs or electrolytes

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

6.3 Shelf life

4 Years

Storage precautions of reconstituted product concentrate:
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.

Chemical and Physical In Use Stability after dilution with Dextrose:
PVC and polyolefin infusion bags: See Table below for recommendations.

Diluent	Dilution	Maximum Duration of Storage at 2-8°C	Maximum Duration of Storage at 25±2°C
5% Dextrose	1 in 2	7 days	48 hours
	1 in 8	7 days	48 hours
	1 in 20	4 days	24 hours
10% Dextrose	1 in 2	48 hours	72 hours
20% Dextrose	1 in 2	48 hours	72 hours

6.4 Special precautions for storage

Storage: Unopened vials of lyophilized material: Do not store above 25°C.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Each vial of AmBisome contains 50 mg of amphotericin B. The vials are packaged in cardboard cartons of 10 vials each.

6.6 Special precautions for disposal and other handling

READ THIS ENTIRE SECTION CAREFULLY BEFORE BEGINNING RECONSTITUTION.

AmBisome is NOT interchangeable with other amphotericin products.

AmBisome 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 AmBisome.

AmBisome 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, AmBisome should be administered through a separate line.

Do NOT mix AmBisome with other drugs or electrolytes.

Aseptic technique must be observed in all handling, since no preservative or bacteriostatic agent is present in AmBisome, or in the material specified for reconstitution and dilution.

AmBisome must be reconstituted by suitably trained staff.

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

1. Add 12 ml of Sterile Water for Injection to each AmBisome vial, to yield a preparation containing 4 mg/ml amphotericin B.

2. IMMEDIATELY after the addition of water, SHAKE THE VIALS VIGOROUSLY for 30 seconds to completely disperse the AmBisome. 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 evidence of precipitation of foreign matter.

3. Calculate the amount of reconstituted (4 mg/ml) AmBisome to be further diluted (see table below).

4. The infusion solution is obtained by dilution of the reconstituted AmBisome with between one (1) and nineteen (19) parts Dextrose solution (5%, 10% or 20%) for infusion 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 AmBisome (see table below).

5. Withdraw the calculated volume of reconstituted AmBisome into a sterile syringe. Using the 5 micron filter provided, instil the AmBisome 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 AmBisome. However, THE MEAN PORE DIAMETER OF THE FILTER SHOULD NOT BE LESS THAN 1.0 MICRON.

Example of the preparation of AmBisome solution for infusion at a dose of 3mg/kg/day in dextrose 5% solution for infusion

Weigh t (kg)	Number of vials	Amount AmBisome (mg) to be withdrawn for further dilution	Volume of reconstituted AmBisome (ml)*	To make up a 0.2mg/ml concentration (1in 20 dilution)		To make up a 2.0mg/ml concentration (1in 2 dilution)	
				Volume of 5% dextrose needed (ml)	Total volume (ml; AmBisome plus 5% dextrose)	Volume of 5% dextrose needed (ml)	Total volume (ml; AmBisome 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 AmBisome (50mg) is reconstituted with 12ml Water for Injection to provide a concentration of 4mg/ml Amphotercin B.

For single use only. Discard any unused contents.

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

License Number: 28192
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