Certificado Número:PP10158347

ORGANISMO REGULADOR DE MEDICINAS Y PRODUCTOS SANITARIOS

En nombre del Departamento de Salud

CERTIFICADO DE UN PRODUCTO FARMACÉUTICO (1)

Este certificado conforma con el formato recomendado por la OrganizaciónMundial de la Salud (se adjuntan las notas explicativas)

País exportador (certificando): **REINO UNIDO**

País importador: **COLOMBIA**

1 Nombre y forma de dosificación del producto:

A) En el Reino Unido - AmBisome 50mg Powder for Solution for Infusion, POWDER FOR INJECTION

B) En COLOMBIA - AmBisome 50mg Powder for Solution for Infusion, POWDER FOR INJECTION

1.1 Ingrediente(s) (2) activo(s) (3) y cantidad por unidad:

Ingrediente(s) activo(s)	Cantidad por unidad
AMPHOTERICIN B	50.000 MG

Para una composición cualitativa completa incluir excipientes, ver adjunto. (4)

1.2 ¿Tiene este producto licencia para comercializarse en el mercado para su empleo en el país exportador? (5) Si

1.3 ¿En la actualidad se encuentra este producto en el mercado del país exportador? Si

1.4 El producto no se comercializa en el país exportador debido a

No aplicable

2A.1 Autorización de Licencia/Comercialización del Producto

Número [7]: **PL 16807/0001**
Fecha de emisión: 11 September 1998

2A.2 El nombre y la razón social del titular de la Autorización de la Licencia/Comercialización del Producto son:

Nombre: GILEAD SCIENCES INTERNATIONAL LIMITED

Razón social: GRANTA PARK, ABINGTON, CAMBRIDGE, CB21 6GT, UNITED KINGDOM

2A.3 Estado del titular de la Autorización de Licencia/Comercialización del producto [8]:

c) no está implicado en la fabricación, envase o etiquetado de la forma de la dosificación pero es responsable de la calidad y emisión del producto

2A.3.1 Para las categorías b, c y d los nombres y las razones sociales de la planta de fabricación donde se produce la forma de la dosificación son [9]:

Ver página adjunta para Fabricantes/Envasadores

2A.4 ¿Se adjunta el Resumen de las Bases de Aprobación? [10] No

2A.5 ¿Está la información adjunta sobre el producto oficialmente aprobada y en consonancia con la licencia? [11] Si

2A.6 Solicitante del certificado, si fuese distinto al poseedor de la licencia (nombre y razón social) [12] :

Nombre: GILEAD SCIENCES IRELAND UC

Razón social: IDA BUSINESS & TECHNOLOGY PARK, CARRIGTOHILL, COUNTY CORK, IRELAND

La sección 2B no está incluida porque el producto mencionado en este certificado tiene licencia en el Reino Unido [6]

3	¿Organiza la autoridad certificadora inspecciones periódicas de la planta de fabricación en la cual se produce la forma de la dosificación? (14)	Si

SI NO O NO ES APLICABLE PASAR A LA PREGUNTA 4

3.1	Periodicidad de las inspecciones rutinarias (años):	3
3.2	¿Ha sido inspeccionado el fabricante de este tipo de forma de dosificación?	Si
3.3	¿Conforman las instalaciones y las operaciones con el GMP como lo recomienda la Organización Mundial de la Salud? (15)	Si
4	¿Satisface la información enviada por el solicitante a la autoridad certificadora todos los aspectos de la fabricación del producto, incluyendo las Buenas Prácticas de Fabricación (GMP)? (16)	Si
	Si no fuese así, explicar	

Información complementaria:

NONE

Dirección de la autoridad certificadora:

Organismo Regulador de Medicinas y productos Sanitarios,
10 South Colonnade, Canary Wharf, London E14 4PU, United Kingdom

Número de teléfono: +44 (0) 20 3080 6593

Nombre de la persona autorizada: Colin Atkinson

Firma:

Sello y fecha: 27 November 2018

30/11/18

Signature Attested by Phillip Jones
Solicitor and Notary
Windsor House, Victoria Street,
Windsor, Berks, SL4 1EN, England,
Tel: 01753 851591

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: Pays / País	United Kingdom of Great Britain and Northern Ireland
This public document Le present acte public / El presente documento público	
2. Has been signed by a été signé par ha sido firmado por	Phillip H Jones
3. Acting in the capacity of agissant en qualité de quien actua en calidad de	Notary Public
4. Bears the seal / stamp of est revêtu du sceau / timbre de y está revestido del sello / timbre de	The Said Notary Public
Certified Atteste / Certificado	
5. at á / en: London	**6. the** le / el día: 03 December 2018
7. by par / por	Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs
8. Number sous no / bajo el numero	APO-1203593
9. Seal / stamp Sceau / timbre Sello / timbre	**10. Signature** Signature Firma: N Larrier

This Apostille is not to be used in the UK and only confirms the authenticity of the signature, seal or stamp on the attached UK public document It does not confirm the authenticity of the underlying document Apostilles attached to documents that have been photocopied and certified in the UK confirm the signature of the UK official who conducted the certification only It does not authenticate either the signature on the original document or the contents of the original document in any way

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To verify this apostille go to www verifyapostille service gov uk

Nombres y Razones sociales de los Fabricantes/Envasadores (9)

Fabricantes

Nombre:	GILEAD SCIENCES INCORPORATED
Razón social:	650 CLIFFSIDE DRIVE, SAN DIMAS, CALIFORNIA, CA 91773, UNITED STATES OF AMERICA
Nombre:	JUBILANT HOLLISTERSTIER LLC
Razón social:	3525 NORTH REGAL STREET, SPOKANE, WA, 99207, UNITED STATES OF AMERICA
Nombre:	OSO BIOPHARMACEUTICALS MANUFACTURING LLC
Razón social:	4272, 4240, 4200 BALLOON PARK ROAD, ALBUQUERQUE, NM, 87109, UNITED STATES OF AMERICA

Envasadores

Nombre:	GILEAD SCIENCES IRELAND UC
Razón social:	IDA BUSINESS & TECHNOLOGY PARK, CARRIGTOHILL, COUNTY CORK, IRELAND

Excipiente	Modifier	Cantidad por unidad
HYDROGENATED SOY PHOSPHATIDYL CHOLINE		213.000 MG
SUCROSE		900.000 MG
DISTEAROYLPHOSPHATIDYLGLYCEROL		84.000 MG
CHOLESTEROL		52.000 MG
DISODIUM SUCCINATE HEXAHYDRATE		27.000 MG
ALPHA TOCOPHEROL		0.640 MG
HYDROCHLORIC ACID	QS	
SODIUM HYDROXIDE	QS	
METHYL ALCOHOL	ND	
WATER FOR INJECTION	QS	

Notas Explicativas

1. Este certificado, en la forma recomendada por la OMS, establece el estado del producto farmacéutico y del solicitante del certificado en el Reino Unido. Es para un único producto solamente puesto que las disposiciones de fabricación e información aprobadas para distintas formas de dosificación y distintas cantidades pueden variar.

2. Cuando sea posible han de utilizarse los Nombres Internacionales No propietarios (INN) o los nombres nacionales no propietarios.

3. La fórmula (composición completa) de la forma de dosificación deberá darse o adjuntarse al certificado.

4. Se prefieren los datos de la composición cuantitativa pero su provisión está sujeta a la disposición del titular de la Autorización de Comercialización.

5. Cuando sea aplicable, adjuntar los datos de cualquier restricción aplicada a la venta, distribución o administración del producto que se especifica en la Autorización de Comercialización.

6. Las secciones 2A y 2B son mutuamente exclusivas.

7. Indicar cuando sea aplicable si la licencia es provisional o el producto todavía no ha sido aprobado.

8. Especificar si la persona responsable de introducir el producto en el mercado:

   (a) fabrica la forma de la dosificación y es responsable de asegurar la calidad y emitir el producto.
   (b) los envases y/o etiquetas de una forma de dosificación fabricado por otra compañía pero es responsable de asegurar la calidad y emisión del producto.
   (c) no está asociado con la fabricación, envasado o etiquetado de la forma de dosificación pero es responsable de la calidad y emisión del producto.
   (d) no está asociado con ninguna de las anteriores.

9. Esta información es opcional y puede proporcionarse únicamente con el permiso del titular de la licencia del producto o en caso de productos no registrados, el solicitante. Si no se completa esta sección, indica que la parte concerniente no ha acordado la inclusión de esta información.

   Deberá tenerse en cuenta que:

   la información concerniente a la planta de fabricación es parte de la Autorización de Comercialización. Si la planta de fabricación cambia, debe actualizarse la licencia o la misma dejará de ser válida.

   en el Reino Unido, la fabricación de productos farmacéuticos sólo se permite en plantas de fabricación autorizadas. Cuando el titular de la licencia del producto o el solicitante conforma los estados (b), (c) o (d) como se describe en la nota 8 anterior el titula de la Licencia de Comercialización es responsable de la fabricación de la forma de la dosificación.

10. Éste se refiere al documento preparado por alguna autoridad normativa nacional que resume las bases técnicas sobre las cuales tiene licencia el producto. La Organismo Regulador de Medicinas y productos Sanitarios del Reino Unido no prepara dicho documento.

11. Éste se refiere a la información del producto aprobado por la Organismo Regulador de Medicinas y productos Sanitarios como un Resumen de las Características del Producto (SPC).

12. En estas circunstancias se requiere permiso de emisión del certificado del titular de la Autorización de Comercialización. Este permiso debe proporcionarlo el solicitante a la Organismo Regulador de Medicinas y productos Sanitarios.

13. Indicar la razón ofrecida por el solicitante para no pedir el registro:

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(a) el producto ha sido desarrollado exclusivamente para el tratamientos de estados - particularmente enfermedades tropicales - no endémicas en el Reino Unido.

(b) el producto ha sido formulado con el criterio de mejorar su estabilidad bajo condiciones tropicales.

(c) el producto ha sido reformulado para excluir excipientes no aprobados para su empleo en productos farmacéuticos en el Reino Unido.

(d) el producto ha sido reformulado para satisfacer un límite distinto de dosificación máxima para un ingrediente activo.

(e) este tipo de producto no precisa Autorización de Comercialización en el Reino Unido.

(f) cualquier otra razón.

14. "Sí" significa que la Organismo Regulador de Medicinas y productos Sanitarios dispone inspecciones periódicas de la planta de fabricación en la cual se produce la forma de dosificación. "No" significa que la fabricación tiene lugar en un país que no es el Reino Unido y las inspecciones no las realiza ninguna Autoridad Normativa. "No Aplicable" significa que la fabricación se produce en un país que no es el Reino Unido y las inspecciones se realizan bajo la tutela del país de fabricación.

15. Los requerimientos de buena práctica en la fabricación y control de calidad de drogas a los que se hace referencia en el certificado son los incluidos en el informe treinta y dos de Comite de Expertos sobre Especificaciones de Preparados Farmacéuticos (OMS Technical Report Series, Nº 823. 1992, Anexo 1). Recomendaciones específicamente aplicables a los productos biológicos formulados por el Comite de Expertos de la OMS sobre Estandarización Biológica (OMS Technical Report Series Nº 822. 1992. Anexo 1).

16. Esta sección tiene que completarse cuando el titular de la licencia del producto o el solicitante conformen el estado (b), (c) o (d) como se describe en la nota 8 anterior. Es de particular importancia cuando los contratistas extranjeros están implicados en la fabricación del producto. En esas circunstancias el solicitante deberá proporcionar a la autoridad certificadora la información para identificar a las partes contratantes responsables de cada etapa de la fabricación de la forma de dosificación acabada y la extensión y naturaleza de cualquier control ejercido sobre cada una de esas partes.

SUMMARY OF PRODUCT CHARACTERISTICS

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1 NAME OF THE MEDICINAL PRODUCT

AmBisome 50 mg Powder for solution 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.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sterile, powder for solution for infusion.

Yellow lyophilised cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AmBisome 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 AmBisome include: disseminated candidiasis, aspergillosis, mucormycosis, chronic mycetoma, cryptococcal meningitis and visceral leishmaniasis.

AmBisome 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

Posology

Treatment of mycoses

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. Data are presently insufficient to define total dosage requirements and duration of treatment necessary for resolution of mycoses. However, a cumulative dose of 1.0 - 3.0 g of amphotericin B as AmBisome over 3 - 4 weeks has been typical. Dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient.

Mucormycosis

The recommended starting dose is 5 mg/kg/day. 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.

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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 AmBisome 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 AmBisome doses (see section 4.4).

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 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 AmBisome, without reports of unusual adverse events. AmBisome 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.

AmBisome 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

AmBisome 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

AmBisome should be administered by intravenous infusion over a 30 - 60 minute period. 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 AmBisome.

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 AmBisome therapy.

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4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions

Anaphylaxis and anaphylactoid reactions have been reported in association with AmBisome infusion. Allergic type reactions, including severe infusion-related reactions can occur during administration of amphotericin-containing products, including AmBisome (see section 4.8). Therefore, administration of a test dose is still advisable before a new course of treatment. For this purpose a small amount of an AmBisome infusion (e.g. 1 mg) can be administered for about 10 minutes, the infusion 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 AmBisome dose can be continued. If a severe allergic or anaphylactic/anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of AmBisome.

Infusion-related reactions

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 their prevention or treatment.

Renal toxicity

AmBisome 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 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, 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 (see section 4.5). 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 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.

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

AmBisome contains approximately 900 mg of sucrose in each vial. This should be taken into account when treating diabetic patients.

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:

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Nephrotoxic medications: Concurrent administration of AmBisome 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, 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: No evidence of benefit from the use of flucytosine with AmBisome 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.

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 AmBisome 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 AmBisome in pregnancy.

AmBisome 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 AmBisome is excreted in human breast milk. A decision on whether to breastfeed while receiving AmBisome 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 AmBisome therapy for the mother.

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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

Summary of adverse reactions

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 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,

Nervous system disorders

Common: headache

Uncommon: convulsion

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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,

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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 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 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 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.

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 AmBisome (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 AmBisome (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 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

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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 haematological status. Haemodialysis or peritoneal dialysis does not appear to affect the elimination of AmBisome.

Special populations (including paediatric population):

No additional information is available in special populations.

5 PHARMACOLOGICAL PROPERTIES

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

Invasive candidiasis

AmBisome (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. AmBisome and Micafungin were administered for a median duration of 15 days. The favourable overall response was 89.5% (170/190) in the AmBisome 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 AmBisome 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).

Paediatric population

The pharmacodynamic profile of AmBisome in paediatric patients is consistent with that described in adult patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of AmBisome (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 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 (Cmax) 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:

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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 (CI)	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 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 ($t_{½\beta}$) 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).

5.3 Preclinical safety data

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

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

Carcinogenicity studies have not been conducted with L-AmB.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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 incompatible with saline solutions and may 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

Shelf –life of AmBisome after first opening

As AmBisome does not contain any bacteriostatic agent, from a microbiological point of view, the reconstituted or diluted product should be used immediately.

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.

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

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 freeze
DO NOT STORE partially used vials for future patient use.

Shelf-life after dilution with Dextrose:
PVC or Polyolefin infusion bags: 25±2°C exposed to ambient light or at 2-8°C. Do not freeze. See table below for recommendations.

Diluent	Dilution	Concentration of Amphotericin B mg/mL	Maximum duration of storage at 2-8°C	Maximum duration of storage at 25±2°C
5% Dextrose	1 in 2	2.0	7 days	48 hours
	1 in 8	0.5	7 days	48 hours
	1 in 20	0.2	4 days	24 hours
10% Dextrose	1 in 2	2.0	48 hours	72 hours
20% Dextrose	1 in 2	2.0	48 hours	72 hours

6.4 Special precautions for storage

AmBisome: Unopened vials; Do not store above 25°C. Keep the container in the outer carton.

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

6.5 Nature and contents of container

AmBisome is presented in 15 ml, 20ml or 30ml sterile, Type I glass vials. The closure consists of a grey butyl rubber stopper and aluminium ring seal fitted with a removable plastic cap. Single-dose vials are packed ten per carton with 10 filters. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

READ THIS ENTIRE SECTION AND SECTION 4.4 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.



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Do NOT mix AmBisome with other medicinal products or electrolytes.

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

AmBisome must be reconstituted by suitably trained staff.

Vials of AmBisome containing 50 mg of amphotericin 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.
2. IMMEDIATELY after the addition of water, SHAKE THE VIAL 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 any 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 by volume, to give a final concentration in the recommended range of 2.00 mg/ml to 0.20 mg/ml amphotericin as AmBisome (see table below).
5. Withdraw the calculated volume of reconstituted AmBisome into a sterile syringe. Using the 5 micron filter provided, instill 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.

Weight (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 (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; 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

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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 amphotericin B.

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

7 MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited,

Granta Park,

Abington,

Cambridge,

CB1 6GT.

8 MARKETING AUTHORISATION NUMBER(S)

PL 16807/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

27/03/2017