

A. PACKAGE LEAFLET

Package leaflet: Information for the user

AmBisome Liposomal 50 mg Powder for dispersion for infusion Liposomal amphotericin B

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AmBisome is and what it is used for
2. What you need to know before you are given AmBisome
3. How to use AmBisome
4. Possible side effects
5. How to store AmBisome
6. Content of the pack and other information

1. What AmBisome is and what it is used for

AmBisome is an antifungal antibiotic. The active ingredient in AmBisome is amphotericin B.

AmBisome is given as an infusion into a vein (a drip) in hospital by a doctor or nurse.

AmBisome is used to treat serious infections caused by fungi:

- **Fungal infections of one or more deep organs of the body.**
- **Suspected fungal infections** in patients with a **raised temperature and neutropenia.** Neutropenia is a reduced number of white blood cells called neutrophils. These are important in fighting infections. Neutropenia can be a side effect of cancer treatments.

Before you are given AmBisome your doctor will check that your fever is not due to bacteria or viruses. You will probably have had one or more antibiotics already. A fever which continues despite treatment may be due to a fungal infection. It's difficult to confirm this with current tests, however.

- **Visceral leishmaniasis**, a disease caused by a parasite.

2. What you need to know before you are given AmBisome

Before your first treatment

Before your first treatment your doctor may give you a small amount of AmBisome. They will then wait for approximately 30 minutes to see whether you have an allergic reaction, before continuing the infusion of the full dose.

Your doctor will not give you AmBisome

- **If you are allergic** (hypersensitive) to Amphotericin B or any of the other ingredients of AmBisome. However, if **your condition is life-threatening** you may be given AmBisome if your doctor believes that only AmBisome can help you.
- If you have previously experienced a severe allergic reaction (**anaphylactic or anaphylactoid**) to AmBisome. Symptoms of such immediate and life-threatening allergic reactions include: flushing, itching, sickness, swelling of the face, mouth, tongue and airways, often enough to cause difficulty breathing.

Warnings and precautions

Your doctor will take special care with AmBisome

- **If you have a severe allergic (anaphylactic) reaction.** If this happens your doctor will stop the infusion.
- **If you get other reactions related to the infusion.** If this happens, your doctor may slow down the infusion, so you receive AmBisome over a longer period of time (approximately 2 hours). Your doctor may also give you medicines to prevent or treat infusion-related reactions, such as diphenhydramine (an antihistamine), paracetamol, pethidine (for pain relief) and/or hydrocortisone (an anti-inflammatory medicine that works by reducing the response of your immune system).
- **If you are taking other medicines that may cause kidney damage,** *see Taking other medicines*, right. AmBisome may cause damage to the kidney. Your doctor or nurse will take regular blood samples. This is to test creatinine (a chemical in the blood that reflects kidney function), and electrolyte levels (particularly potassium and magnesium) Both of these can be abnormal if you have kidney problems. This is particularly important if you are taking other medicines that may cause damage to the kidney. The blood samples will also be tested for changes in your liver, and your body's ability to produce new blood cells and platelets.
- **If blood tests show a change in kidney function,** or other important changes. If this happens, your doctor may give you a lower dose of AmBisome or stop treatment.
- **If blood tests show that your potassium levels are low.** If this happens, your doctor may prescribe a potassium supplement for you to take while you are treated with AmBisome.
- **If you have a white blood cell transfusion.** Sudden and severe problems in the lungs can happen if you are given AmBisome infusion during or shortly after a white blood cell transfusion. Your doctor will recommend that the infusions are separated by as long a period as possible. This will reduce the risk of lung problems, and your lungs will be monitored.
- **If you have had kidney failure and are having dialysis.** Your doctor may start AmBisome treatment after the procedure has ended.
- **If you have diabetes.** AmBisome contains approximately 900 mg of sucrose (sugar) in each vial. Tell your doctor if you have diabetes.

Other medicines and AmBisome

Tell your doctor if you are taking any other medicines, or have recently taken any. This includes medicines and herbal products you bought without a prescription.

Medicines that may cause kidney damage:

- **Medicines that suppress the immune system** (*immunosuppressants*), such as ciclosporin and tacrolimus.
- **Certain antibiotics** called *aminoglycosides* (including gentamicin, neomycin and streptomycin) and *polymyxins*.

- **Pentamidine** a medicine used to treat pneumonia in people with AIDS and leishmaniasis.
- ↳ **Tell your doctor if you are taking any of these medicines.** AmBisome may make any kidney damage caused by the medicine worse. If you are taking any of these medicines, your doctor or nurse will take regular blood samples to check your kidneys.

Medicines that may lower your potassium levels:

- **Corticosteroids**, anti-inflammation medicines that work by reducing the response of your immune system.
- **Corticotropin (ACTH)**, used to control the amount of corticosteroid produced by your body. The body produces corticosteroid in response to stress.
- **Diuretics**, medicines that increase the amount of urine your body produces. This includes furosemide.
- **Digitalis glycosides**, medicines produced from the foxglove plant and used to treat heart failure. AmBisome may worsen the side effects of digitalis, such as heart rhythm changes.
- **Muscle relaxants** usually used during surgery, such as tubocurarine. AmBisome may increase the muscle relaxant effect.

Other medicines:

- **Antifungal medicines**, such as flucytosine. AmBisome may worsen the side effects of flucytosine. This includes changes in the body's ability to produce new blood cells. This may be seen in blood tests.
- **Certain cancer medicines**, such as methotrexate, doxorubicin, carmustine and cyclophosphamide. Taking this type of medicine with AmBisome may cause kidney damage, wheezing or trouble breathing and low blood pressure.
- **White blood cell (leukocyte) transfusions.** Sudden and severe problems in the lungs can happen if you are given AmBisome infusion during or shortly after a white blood cell transfusion. Your doctor will recommend that the infusions are separated by as long a period as possible. This will reduce the risk of lung problems and your lungs will be monitored.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Your doctor will only prescribe AmBisome if they think the benefits of treatment outweigh the risks to you and your unborn child or your baby.

Driving and using machines

Do not drive or operate machinery

Some of the possible side effects of AmBisome could affect your ability to drive or use machines safely, See Section 4, *Possible side effects*.

AmBisome contains sugar

Tell your doctor if you have diabetes. AmBisome contains approximately 900 mg of sugar (sucrose) in each vial.

3. How AmBisome is given

AmBisome is always given to you by a doctor or nurse. It is given into a vein (a drip). AmBisome must not be given by any other method.

To prepare the infusion AmBisome must be dissolved in sterile water for injection and then diluted with a solution containing dextrose.

AmBisome must not be mixed with saline (salt) solutions or with other medicinal products or electrolytes.

AmBisome is not interchangeable with other amphotericin products.

Before your first treatment

Before your first treatment your doctor may give you a small amount of AmBisome. They will then wait for approximately 30 minutes to see whether you have an allergic reaction, before continuing the infusion of the full dose.

Use in adults

Your dose of AmBisome will depend on your body weight.

Fungal infections of one or more deep organs of the body:

Treatment is normally started at 1 mg per kg of body weight, every day over 2 to 4 weeks.

Your doctor may decide to increase the amount you receive to as high as 3 mg per kg of body weight.

For mucormycosis the starting dose is normally 5 mg per kg of body weight per day. The duration of therapy will be determined on an individual basis by your Doctor.

Suspected fungal infections in patients with a raised temperature and neutropenia: The recommended daily dose is 3 mg per kg of body weight, per day. AmBisome will be given to you until your temperature is normal for 3 days in a row. However, AmBisome must not be given for more than 42 days in a row.

Visceral leishmaniasis:

You may be given a total dose of between 21 and 30 mg per kg of body weight, over a period of 10 to 21 days. Your doctor will decide on the amount of AmBisome you will receive and over how many days it will be given.

Use in children and adolescents

AmBisome has been used to treat children. The dose of AmBisome for a child is calculated per kg of body weight in the same way as for adults.

AmBisome is not recommended in babies under 1 month old.

Use in elderly patients

No change in dose or frequency of infusion is needed for elderly patients.

Use in patients with kidney problems

AmBisome has been given to patients with kidney problems at doses ranging from 1 to 5 mg per kg of body weight per day. No change in dose or frequency of infusion is required. Your doctor or nurse will take regular blood samples to test for changes in kidney function during AmBisome treatment.

How long will the infusion take?

Normally the infusion will take 30 to 60 minutes. For doses greater than 5 mg per kg of body weight per day, the infusion could take up to 2 hours.

If you receive a higher dose of AmBisome than you should

You should tell your doctor immediately if you think you received too much AmBisome. If you have any further questions on the use of this product, ask your doctor.

4. Possible side effects

Like all medicines, AmBisome can cause side effects, although not everybody gets them.

Side effects during the infusion

You may get side effects during the infusion:

- **Very common** (*These can affect more than 1 in every 10 people*): fever, chills, and shivering.
- **Less frequent infusion-related side effects include:** chest tightness, chest pain, breathlessness, difficulty breathing (*possibly with wheezing*), flushing, a faster heart rate than normal, low blood pressure and musculoskeletal pain (described as joint pain, back pain, or bone pain).

These side effects clear up quickly when the infusion is stopped. These reactions may not happen with future infusions of AmBisome or with a slower infusion (over 2 hours). Your doctor may give you other medicines to prevent infusion-related reactions, or to treat the symptoms if you do get them. If you have a severe infusion-related reaction, your doctor will stop the AmBisome infusion and you should not receive this treatment in the future.

Very common side effects

These can affect more than 1 in every 10 people:

- Low blood potassium levels, leading to feeling tired, confused, having muscle weakness or cramps
- Feeling sick or being sick
- Fever, chills or shivering.

Common side effects

These can affect up to 1 in every 10 people:

- Low magnesium, calcium or sodium blood levels, leading to feeling tired, confused, muscle weakness or cramps
- High blood sugar levels
- Headache
- A faster heart rate than normal
- Widening of the blood vessels, causing low blood pressure and flushing
- Breathlessness
- Diarrhoea
- Stomach (abdominal) pain
- Rash
- Chest pain
- Back pain
- Abnormal results for liver or kidney function showing up in blood tests or urine tests.

Uncommon side effects

These can affect up to 1 in every 100 people:

- Bleeding into the skin, unusual bruising and bleeding for a long time after injury

- Severe allergic (anaphylactoid) reaction
- Fits or seizures (convulsions)
- Difficulty breathing, possibly with wheezing.

Other side effects

It is not known how frequently these side effects occur:

- Anaemia (low red blood cell levels), with symptoms of excessive tiredness, being out of breath after light activity, and a pale complexion
- Severe allergic (anaphylactic) or sensitivity reactions
- Heart attacks and heart rhythm changes
- Kidney failure and kidney problems. Signs include tiredness and passing less urine
- Severe swelling of the skin around the lips, eyes or tongue.
- Breakdown of muscle
- Bone pain and joint pain

Interference with Phosphorus blood test results. False readings showing an increase in the levels of phosphate in your blood may occur when samples from patients receiving AmBisome are analyzed using a specific system called a PHOSm assay.

If your test results show high levels of phosphate, then further analysis using a different system may be necessary to confirm the results.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

5. How to store AmBisome

AmBisome is stored in the hospital pharmacy.

Keep this medicine out of the sight and reach of children.

Do not use AmBisome after the date which is stated on the label after {EXP}. The expiry date refers to the last day of the month.

Do not store above 25°C.

Do not store partially used vials for future patient use.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What AmBisome contains

The active ingredient is *amphotericin B*. Each vial contains 50 mg of amphotericin B enclosed inside liposomes (small fat particles).

The other ingredients are: hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol, alpha tocopherol, sucrose (sugar), disodium succinate hexahydrate, sodium hydroxide and hydrochloric acid.

What AmBisome looks like and contents of the pack

AmBisome is a sterile, bright yellow lyophilisate (freeze-dried powder) for dispersion for infusion.

It is presented in a 15-ml, 20-ml or 30-ml glass vial.

Each vial contains 50 mg of the active ingredient amphotericin B.

The closure consists of a rubber stopper and an aluminium ring seal fitted with a removable plastic cap.

Each carton contains 10 vials and 10 filters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Gilead Sciences International Ltd
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Manufacturer
Gilead Sciences Ireland UC,
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in
September 2020

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The following information is intended for healthcare professionals only:

READ THIS ENTIRE SECTION AND SECTION 4.4 CAREFULLY BEFORE BEGINNING RECONSTITUTION

AmBisome is not equivalent to 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 medicinal products or electrolytes.

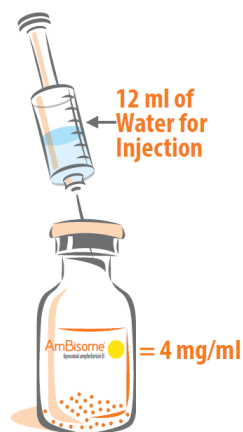
Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in AmBisome, or in the materials specified for reconstitution and dilution.

AmBisome must be reconstituted by suitably trained staff.

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

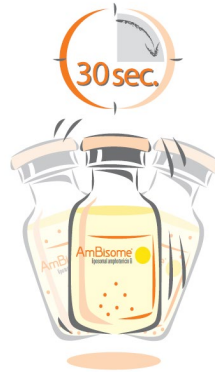
1. Add 12 ml of Sterile Water for Injection to each AmBisome vial, to yield a preparation containing 4 mg/ml amphotericin B.

Step 1



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.

Step 2

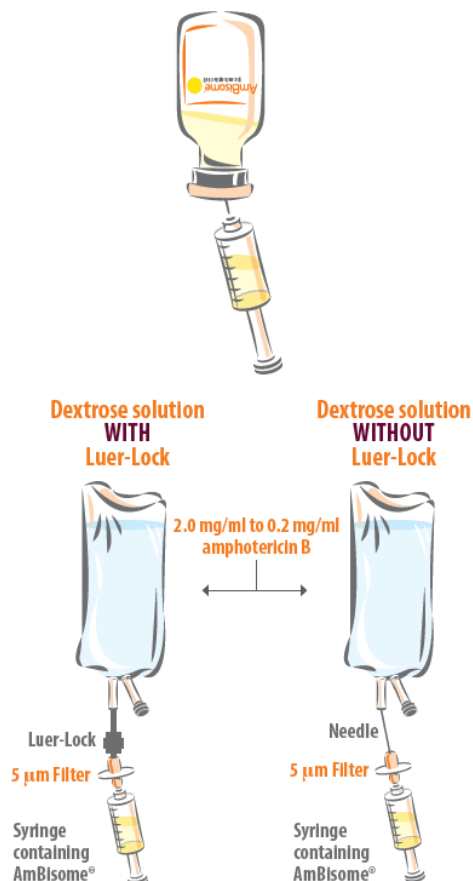


3. Calculate the amount of reconstituted AmBisome (4 mg/ml) to be further diluted (see table below).

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 B 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.

Step 5



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 dispersion 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
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.

Instruction video on reconstitution and dilution:
www.medicines.org.uk/emc/product/1022/video

