PACKAGE LEAFLET

Package leaflet: Information for the user

Amphotericin B liposomal Tillomed 50 mg powder for concentrate for dispersion for infusion

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Amphotericin B liposomal Tillomed is and what it is used for

What is Amphotericin B liposomal Tillomed

Amphotericin B liposomal Tillomed contains the active substance amphotericin B. Amphotericin B liposomal Tillomed is an antifungal antibiotic, which is a medicine used to treat serious fungal infections.

Amphotericin B liposomal Tillomed is used for:

• Treatment of severe systemic and/or deep-seated fungal infections (mycoses);

• Empirical treatment of patients with low neutrophil counts (decreased numbers of white blood cells, neutropenia) suspected of having a fungal infection and presenting with fever.

Amphotericin B liposomal Tillomed can be used as secondary therapy for visceral leishmaniasis (*Leishmania donovani*) in immunocompetent patients and in patients with a compromised immune system (e.g. people living with HIV). Recurrences must be expected in patients with a compromised immune system. There is no experience in recurrence prevention.

2. What you need to know before you are given Amphotericin B liposomal Tillomed

Do not use Amphotericin B liposomal Tillomed

- If you are allergic to amphotericin B or any of the other ingredients of Amphotericin B liposomal Tillomed listed in section 6.
- Amphotericin B liposomal Tillomed contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

Warnings and precautions

Talk to your doctor or pharmacist before using Amphotericin B liposomal Tillomed.

Take special care with the use of Amphotericin B liposomal Tillomed:

- 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 Amphotericin B liposomal Tillomed 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), acetaminophen, 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 the section *Other medicines and Amphotericin B liposomal Tillomed*. Amphotericin B liposomal Tillomed may cause damage to the kidney. Your doctor or nurse will take blood samples to measure your creatinine (a chemical in the blood that reflects kidney function), and electrolyte levels (particularly potassium and magnesium) before and during the treatment with Amphotericin B liposomal Tillomed because both of these can be abnormal if you have changes in your kidney function. This is particularly important if you have previous renal damage or if you are taking other medicines that can affect the way your kidney functions. 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, your doctor may give you a lower dose of Amphotericin B liposomal Tillomed 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 Amphotericin B liposomal Tillomed;
- If blood test shows that your potassium levels are high, you may suffer irregular heartbeat, sometimes severe.
- If you have a white blood cell transfusion. If you are having an infusion of Amphotericin B liposomal Tillomed during or shortly after a white blood cell transfusion, you may experience sudden and serious problems in your lungs. 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 any of the above apply to you, your doctor may decide to alter your treatment.

Other medicines and Amphotericin B liposomal Tillomed

Tell your doctor if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

The following medicines that are known to interact with amphotericin B may also interact with Amphotericin B liposomal Tillomed.

- Medicines that may cause kidney damage:
  - medicines that suppress the immune system (*immunosuppressants*), such as ciclosporin;
  - certain antibiotics called *aminoglycosides* (including gentamicin, neomycin and streptomycin);
  - pentamidine, a medicine used to treat inflammation of the lungs (pneumonia) in patients with AIDS or leishmaniasis.

  ➥ Tell your doctor if you are taking any of these medicines. These medicines can cause kidney damage which Amphotericin B liposomal Tillomed may make worse. If you are taking any of these medicines, your doctor or nurse will take regular blood samples to check your kidney function.

- 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 regulate the body's natural production of corticosteroids 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 (Digitalis purpurea) and used to treat heart failure. Amphotericin B liposomal Tillomed can reduce the level of potassium in the blood, which in turn can worsen the side effects of digitalis (irregular heartbeat);
  - muscle relaxants, such as tubocurarine. Amphotericin B liposomal Tillomed may increase the muscle relaxant effect.

➥ Tell your doctor if you are taking any of these medicines

- Other medicines:
  - antifungal medicines (medicines used to treat fungal infections), such as flucytosine. Amphotericin B liposomal Tillomed 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 Amphotericin B liposomal Tillomed 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 Amphotericin B liposomal Tillomed 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.

➥ Tell your doctor if you are taking any of these medicines.

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.

The safety of using liposomal amphotericin B during pregnancy has not been proven. If you are pregnant, your doctor will only prescribe Amphotericin B liposomal Tillomed for you if the expected benefit of the treatment to you and the unborn child outweighs the possible risk.

It is not known whether liposomal amphotericin B passes into breast milk. The decision to breastfeed during treatment with Amphotericin B liposomal Tillomed should take into account the potential risk to the child, the benefit of breastfeeding to the child, and the benefit of Amphotericin B liposomal Tillomed therapy to the mother.

Driving and using machines

Some of the possible side effects of Amphotericin B liposomal Tillomed may affect your ability to drive or use machines safely, See Section 4, *Possible side effects*.

Amphotericin B liposomal Tillomed contains sodium

This medicine contains less than 1 mmol (23 mg) sodium per vial/dose, that is to say essentially 'sodium-free'.

3. How to use Amphotericin B liposomal Tillomed

Amphotericin B liposomal Tillomed is always given to you by a doctor or nurse.

Liposomal amphotericin B is NOT interchangeable with non-liposomal amphotericin B formulations.

To prepare the dispersion for infusion, Amphotericin B liposomal Tillomed must be dissolved in sterile water for injection and then diluted with a solution containing glucose. It is given into a vein (a drip). Amphotericin B liposomal Tillomed must not be given by any other method.

Amphotericin B liposomal Tillomed must not be mixed with saline (salt) solutions or with other medicinal products or electrolytes (see section 'information is intended for healthcare professionals only' of the PIL).

Use in adults

Your dose of Amphotericin B liposomal Tillomed will depend on your body weight and is individually adjusted to your needs.

The medicine is intended for intravenous infusion after reconstitution and dilution.

Usually, the infusion time is 30-60 minutes. Lower infusion rates (over 2-hour periods), particularly at higher daily doses, may be considered to reduce the risk of infusion reactions.

Treatment of mycoses:

Usually, you will be administered Amphotericin B liposomal Tillomed at a dose of 3 mg per kg body weight per day. For the treatment of *Aspergillus* infections, your dose may be gradually increased to 5 mg/kg/day.

Mucormycosis: You will usually be administered Amphotericin B liposomal Tillomed at a dose of 5-10 mg/kg/day.

Empirical treatment when a fungal infection is suspected:

You will usually be administered Amphotericin B liposomal Tillomed at a dose of 3 mg/kg/day.

Treatment of visceral leishmaniasis:

Your doctor will use national and international treatment recommendations to determine the appropriate dose and treatment interval for you. Usually, the dose is between 3 and 5 mg/kg/day. The duration of treatment is 10 to 38 days, depending on the chosen treatment regimen and whether you are co-infected with HIV.

Use in patients with kidney problems

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 Amphotericin B liposomal Tillomed treatment.

If you have had kidney failure and are having dialysis. Your doctor may start Amphotericin B liposomal Tillomed treatment after the procedure has ended.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

Use in children and adolescents

This medicine is used to treat children from one month old to 18 years of age. The dose is individual and based on body weight, in the same way as for adults.

Amphotericin B liposomal Tillomed is not recommended in infants under 1 month old.

4. Possible side effects

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

Side effects during the infusion

You may get side effects during the infusion:

- Very common (may affect more than 1 in 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 Amphotericin B liposomal Tillomed 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 Amphotericin B liposomal Tillomed infusion and you should not receive this treatment in the future.

Very common (may affect more than 1 in 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 (may affect up to 1 in 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.
- high blood potassium levels

Uncommon (may affect up to 1 in 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.

<u>Other side effects</u>

Not known (frequency cannot be estimated from the available data)
- 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 Amphotericin B liposomal Tillomed 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 or pharmacist. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Amphotericin B liposomal Tillomed

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

Do not use this medicine after the expiry date which is stated on the vial label and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Shelf –life of after reconstitution/dilution

As Amphotericin B liposomal Tillomed does not contain any bacteriostatic agent, from a microbiological point of view, the reconstituted or diluted medicinal 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.

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

Shelf-life after reconstitution

Glass vials for 48 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 solution for injection

PVC infusion bag: 25 ± 2°C or 2 - 8°C. Do not freeze.

See table below for recommendations:

Diluent	**Concentration**	**Concentration of Amphotericin B mg/mL**	**Maximum duration of storage at 2-8°C**	**Maximum duration of storage at 25±2°C**

Dextrose 50 mg/mL (5%) solution for infusion	1 :2	2.0	7 days	72 hours
	1:8	0.5	7 days	72 hours
	1:20	0.2	4 days	24 hours
Dextrose 100 mg/mL (10%) solution for infusion	1:2	2.0	48hours	72 hours
Dextrose 200 mg/mL (20%) solution for infusion	1:2	2.0	48 hours	72 hours

Polyolefin infusion bags: 25 ± 2°C or 2 - 8°C. Do not freeze.

See table below for recommendations:

Diluent	**Concentration**	**Concentration of Amphotericin B mg/mL**	**Maximum duration of storage at 2 - 8°C**	**Maximum duration of storage at 25 ± 2°C**
Dextrose 50 mg/mL (5%) solution for infusion	1 :2	2.0	7 days	24 hours
	1:8	0.5	7 days	24 hours
	1:20	0.2	7 days	24hours
Dextrose 100 mg/mL (10%) solution for infusion	1:2	2.0	48hours	
	1:20	0.2	48 hours	
Dextrose 200 mg/mL (20%) solution for infusion	1:2	2.0	48 hours	

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

6. Contents of the pack and other information

What Amphotericin B liposomal Tillomed contains

The active substance is amphotericin B. Each vial contains 50 mg of amphotericin B in liposomes (small fat particles). After reconstitution, 1 ml of the concentrate contains 4 mg amphotericin B.

- The other ingredients are hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol, All-*rac*-α-Tocopherol, sucrose (sugar), disodium succinate hexahydrate, sodium hydroxide (for pH adjustment) and hydrochloric acid, concentrated (37%) (for pH adjustment).

What Amphotericin B liposomal Tillomed looks like and contents of the pack

Amphotericin B liposomal Tillomed is a sterile, yellow-coloured lyophilized powder for concentrate for dispersion for infusion.

It is presented in 20-ml clear glass vials (type I).

The closure consists of a rubber stopper and an aluminium ring seal fitted with a removable blue color plastic cap. Disposable vials are available in cartons with 5-micron filters.
Pack sizes: 1 vial with 1 filter and 10 vials with 10 filters. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Tillomed Pharma GmbH
Mittelstraße 5/5a,
12529 Schönefeld,
Germany

Manufacturer[1]

Tillomed Malta Limited
Malta Life Sciences Park,
LS2.01.06 Industrial Estate,
San Gwann, SGN 3000, Malta

SGS Pharma Magyarorszag Kft.
Derkovits Gyula Utca 53,
Budapest XIX,1193,
Hungary

[1]Only actual manufacturer stated on printed leaflet.

This medicine is authorised in the Member States of the European Economic Area under the following names:

Germany	Amphotericin B liposomal Tillomed 50 mg Pulver für ein Konzentrat zur Herstellung einer Infusionsdispersion
Austria	Amphotericin B liposomal Tillomed 50 mg Pulver für ein Konzentrat zur Herstellung einer Infusionsdispersion
Belgium	Amphotericin B Liposomal Tillomed 50 mg Pulver für ein Konzentrat zur Herstellung einer Infusionsdispersion Amphotericine B Liposomal Tillomed 50 mg poudre pour dispersion à diluer pour dispersion pour perfusion Amfotericine B Liposomaal Tillomed 50 mg Poeder voor concentraat voor dispersie voor infusie
Denmark	Amphotericin B liposomal Tillomed
Greece	Amphotericin B Liposomal/ Tillomed
Finland	Amphotericin B liposomal Tillomed
France	AMPHOTERICINE B LIPOSOMAL TILLOMED 50 mg, poudre pour dispersion à diluer pour dispersion pour perfusion
Ireland	Amphotericin B liposomal Tillomed 50 mg Powder for concentrate for dispersion for infusion
Italy	*FUNGOTILL LIPOSOMIALE*
Malta	Amphotericin B liposomal Tillomed 50 mg Powder for concentrate for dispersion for infusion
Netherlands	Amfotericine B liposomaal Tillomed 50 mg Poeder voor concentraat voor dispersie voor infusie
Norway	Amphotericin B liposomal Tillomed
Sweden	Amphotericin B liposomal Tillomed
Slovenia	Amfotericin B liposomal Tillomed 50 mg prašek za koncentrat za disperzijo za infundiranje
Cyprus	Amphotericin B liposomal Tillomed 50mg Powder for concentrate for dispersion for infusion

This leaflet was last revised in July 2025

The following information is intended for healthcare professionals only:

READ THIS ENTIRE SECTION AND SUMMARY OF PRODUCT CHARACTERISTICS CAREFULLY BEFORE BEGINNING RECONSTITUTION

Due to unique pharmacokinetic properties the product is not equivalent to non-liposomal formulations of amphotericin B.

Amphotericin B liposomal Tillomed must be reconstituted using Sterile Water for Injection (without a bacteriostatic agent) and diluted in Dextrose 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) solution 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 Tillomed.

Amphotericin B liposomal Tillomed is NOT compatible with sodium chloride solution and must not be reconstituted or diluted with sodium chloride solution or administered through an intravenous line that has previously been used for saline unless first flushed with dextrose 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) solution for infusion. If this is not feasible, Amphotericin B liposomal Tillomed should be administered through a separate line.

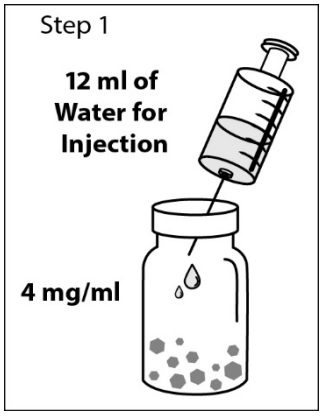
Do NOT mix Amphotericin B liposomal Tillomed with other medicinal products or electrolytes.

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

Amphotericin B liposomal Tillomed must be reconstituted by suitably trained staff.

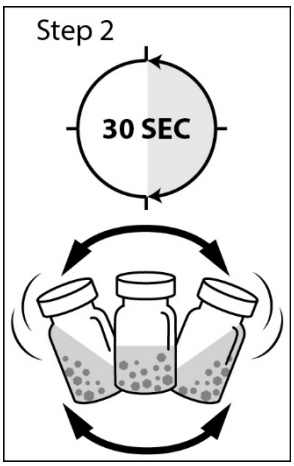
Vials of Amphotericin B liposomal Tillomed containing 50 mg of amphotericin B are prepared as follows:

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

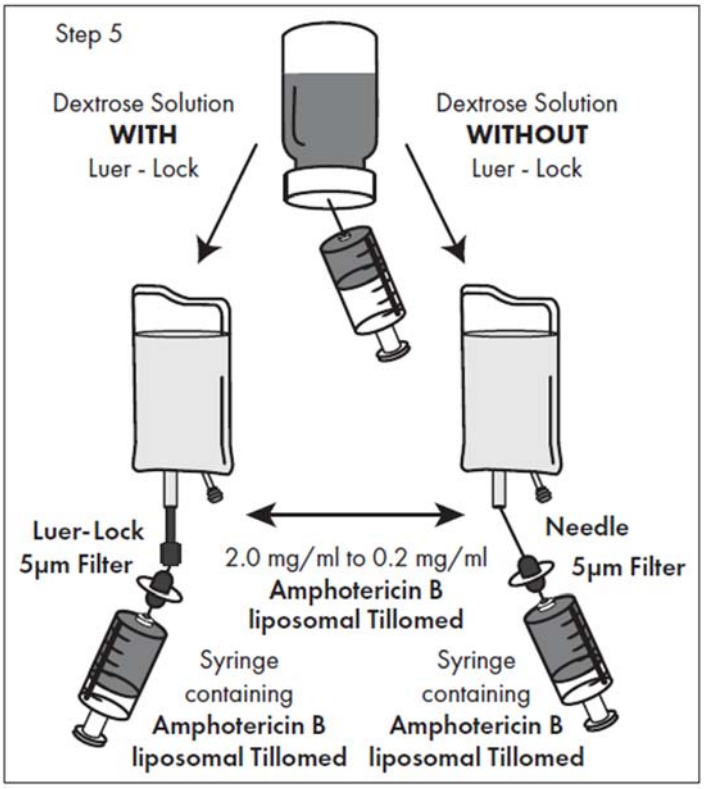


2. IMMEDIATELY after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 SECONDS to completely disperse the Amphotericin B liposomal Tillomed. After reconstitution

the concentrate is a translucent, yellow dispersion. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained but not more than 120 seconds. Do not use if there is any evidence of precipitation of foreign matter.



3. Calculate the amount of reconstituted Amphotericin B liposomal Tillomed (4 mg/ml) to be further diluted.
4. The ready-to-use dispersion for infusion is obtained by diluting reconstituted Amphotericin B liposomal Tillomed with 1-19 volumes of glucose 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) solution for infusion. The final concentration is therefore in the recommended range of 2.0 - 0.2 mg/ml Amphotericin B as Amphotericin B liposomal Tillomed.
5. Withdraw the calculated volume of reconstituted Amphotericin B liposomal Tillomed into a sterile syringe Using the 5-micron filter provided, instil the Amphotericin B liposomal Tillomed preparation into a sterile container with the correct amount of dextrose solution 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) for infusion.



An in-line membrane filter may be used for intravenous infusion of Amphotericin B liposomal Tillomed. However, the mean pore diameter of the filter should not be less than 1.0 micron.

DO NOT keep opened vials for future use.

Since Amphotericin B liposomal Tillomed does not contain any antibacterial agents, it is recommended from a microbiological point of view that the dissolved or diluted medicinal product is used immediately.

The user is responsible for the storage time and storage conditions of the ready-to-use solution before administration. Normally a period of 24 hours at 2-8°C should not be exceeded unless the medicinal product has been prepared under controlled and validated aseptic conditions.

The medicinal product is *for single use only* and *any unused solution should be discarded*. Do not keep opened vials for future use.

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