Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amphotericin B Liposomal Tillomed 50 mg Powder for concentrate for dispersion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of amphotericin B in liposomes. After reconstitution, 1 ml of the concentrate contains 4 mg amphotericin B.

Excipients with known effects:

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

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

powder for concentrate for dispersion for infusion
yellow coloured, sterile lyophilized powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amphotericin B liposomal Tillomed is indicated in adults and paediatric patients aged 1 month and older for:

- Treatment of severe systemic or deep mycoses
- Empirical treatment of suspected fungal infections in febrile neutropenic patients.

Amphotericin B liposomal Tillomed can be used as a secondary therapy for visceral leishmaniasis (*Leishmania donovani*) in immunocompetent patients and in patients with a compromised immune system (e.g. people living with HIV) (see section 4.4). Recurrences must be expected in patients with a compromised immune system. There is no experience in recurrence prevention.
National and international recommendations for the appropriate use of anti-infective substances should be taken into account.

4.2 Posology and method of administration

Posology
Therapy should be initiated by a physician experienced in the management of invasive fungal diseases.
Non-equivalence of amphotericin products:
Different amphotericin products (sodium deoxycholate, liposomal, lipid complex) are not equivalent in terms of pharmacodynamics, pharmacokinetics and dosing. Hence, they should not be used interchangeably without accounting for these differences. Both the trade name, common name and dose should be verified pre-administration.

Adult patients
Treatment of mycoses:
Dose and treatment duration must be tailored to the specific needs of each patient. Treatment is usually started with 3 mg liposomal amphotericin B per kg body weight per day. For the treatment of *Aspergillus* infections, the dose may be gradually increased to 5 mg/kg/day.
Mucormycosis:
In the treatment of mucormycosis, the recommended dose is 5 to 10 mg/kg/day. Avoid slow dose escalation. In case of CNS involvement, high-dose treatment with 10 mg/kg/day should be considered. The required length of treatment for mucormycosis should be individualised according to the extent of disease, the feasibility of complete surgical treatment, severity of immunocompromisation and clinical response evaluations.
Empirical treatment of febrile neutropenic patients:

For the empirical treatment of febrile neutropenic patients with suspected fungal infection, a dose of 3 mg/kg/day is recommended.
Visceral leishmaniasis:
National and international treatment recommendations should be followed. The usual dose is 3 to 5 mg/kg/day with varying treatment intervals. Treatment duration is 10 to 38 days, depending on treatment regimen and HIV-coinfection.

Special populations
Elderly patients:
Dose adjustment is not necessary.
Renal impairment:
Liposomal amphotericin B has been administered in clinical trials to patients with renal impairment at doses ranging from 1 to 5 mg/kg/day without the need to adjust the dose or dosing interval (see section 4.4). Administration during haemodialysis or haemofiltration procedures should be avoided (see section 5.2).
Hepatic impairment:
There are no data available to provide dosing recommendations for patients with hepatic impairment (see section 4.4).
Paediatric population:
The safety and efficacy of liposomal amphotericin B in children aged less than 1 month have not been established. No data are available.

Method of administration
After reconstitution and dilution, Amphotericin B liposomal Tillomed is given as an intravenous infusion over 30-60 minutes. Lower infusion rates (over a 2-hour period), particularly at higher daily doses, may be considered to reduce the risk of infusion reactions (see section 4.4). The recommended concentration for an intravenous infusion is 0.2 - 2 mg/ml amphotericin B in the form of Amphotericin B liposomal Tillomed. Amphotericin B as liposomal amphotericin B has been administered at cumulative doses of 16.8 g over a period of 3 months without causing any toxic reactions.
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, soya, peanut or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions
Anaphylactic and anaphylactoid reactions have been reported with liposomal amphotericin B. In the event of a serious anaphylactic/anaphylactoid reaction, the infusion must be stopped immediately and the patient must not receive any further infusions of Amphotericin B liposomal Tillomed.
Infusion reactions
Other serious infusion reactions may occur with the administration of medicinal products containing amphotericin B, including Amphotericin B liposomal Tillomed (see section 4.8). Although infusion reactions are not usually serious, appropriate precautions to avoid or treat such reactions should be taken in patients treated with Amphotericin B liposomal Tillomed. Lower infusion rates (over 2 hours) and the routine administration of diphenhydramine, paracetamol, pethidine and/or hydrocortisone have been effective in prevention and treatment.
Renal toxicity
Liposomal amphotericin B 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 liposomal amphotericin B 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.
Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium, as well as renal, hepatic and haematopoietic function should be performed. Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of liposomal amphotericin B administration. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Most of them occurred in patients with renal impairment, and some cases after potassium supplementation in patients with previous hypokalaemia. Therefore, renal function and laboratory evaluation of potassium should be measured before and during treatment. This is particularly important in patients with pre-existing renal disease, who have already experienced renal failure, or in patients receiving concomitant nephrotoxic medications (see section 4.5).
Pulmonary toxicity

Acute pulmonary toxicity has been reported in patients receiving conventional amphotericin B (as sodium deoxycholate complex) during or shortly after a leukocyte transfusion. It is therefore recommended to delay infusions as long as possible after this event and to continue to monitoring pulmonary function.
Visceral leishmaniasis
Since there is very limited clinical study data on use of liposomal amphotericin B in visceral leishmaniasis, only use as secondary therapy is currently recommended.
This medicinal product contains less than 1 mmol (23 mg) sodium per vial/dose, that is to say essentially "sodium-free'.
Paediatric population
Due to a lack of data on safety and efficacy, liposomal amphotericin B is not recommended for use in children under one month (life).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with liposomal amphotericin B. However, the following medicinal products are known to interact with amphotericin B and probably also with liposomal amphotericin B:
Nephrotoxic medicinal products: Concomitant administration of liposomal amphotericin B with other nephrotoxic agents (e.g. ciclosporin, aminoglycosides and pentamidine) may enhance the potential for drug-induced nephrotoxicity in some patients. However, a nephrotoxic effects associated with the concomitant administration of ciclosporin and/or aminoglycosides with liposomal amphotericin B have been observed much less frequently than with concomitant administration of conventional amphotericin B. Periodic monitoring of renal function is recommended in patients receiving liposomal amphotericin B concomitantly with other nephrotoxic medicinal products.
Corticosteroids, corticotropin (ACTH) and diuretics: Concomitant use of corticosteroids, corticotropin (ACTH) and diuretics (loop and thiazide diuretics) may exacerbate hypokalaemia.
Digitalis glycosides: Liposomal amphotericin B-induced hypokalaemia may exacerbate digitalis toxicity.
Muscle relaxants: Liposomal amphotericin B-induced hypokalaemia may potentiate the curare-like effect of skeletal muscle relaxants (e.g. tubocurarine).
Antifungals: Concomitant administration of flucytosine may increase flucytosine toxicity, as its cellular uptake may be increased and/or renal excretion may be impaired.
Antineoplastic agents: Concomitant use of antineoplastic agents may increase the potential for nephrotoxicity, bronchospasm and hypotension. Antineoplastic agents should be used with caution.
Leukocyte transfusions: Acute pulmonary toxicity has been reported in patients receiving conventional amphotericin B (as sodium deoxycholate complex) during or shortly after a leukocyte transfusion. It is therefore recommended to delay infusions as long as possible after this event and to continue to monitoring the lung function.

4.6 Fertility, pregnancy and lactation

Pregnancy
Teratogenicity studies in rats and rabbits indicated that liposomal amphotericin B has no teratogenic potential in these species (see section 5.3).
The safety of liposomal amphotericin B in pregnant women has not been established. Liposomal amphotericin B should only be used during pregnancy if the potential benefit outweighs the potential risk to the mother and fetus.
Systemic fungal infections have been successfully treated with conventional amphotericin B with no apparent effect on the fetus, however the number of cases reported is insufficient to draw a conclusion on the safety of liposomal amphotericin B in pregnancy.

Breast-feeding
It is unknown whether amphotericin B is excreted in human breast milk. The decision whether to breastfeed while receiving liposomal amphotericin B should take into account the potential risk to the child, the benefit of breast feeding to the child and the benefit of Amphotericin B liposomal Tillomed therapy for the mother.

Fertility
No adverse effects on male or female reproductive performance in rats were noted (refer section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been conducted on the effects of liposomal amphotericin B on the ability to drive and use machines. Some of the adverse reactions of liposomal amphotericin B listed below may affect the ability to drive and use machines.

4.8 Undesirable effects

Fever and chills are the very common infusion reactions expected with liposomal amphotericin B administration. Uncommon infusion reactions include 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 adverse reactions resolve quickly after the infusion is stopped and may not recur with each subsequent dose or may be absent if the infusion is given at a slow rate (over 2 hours). Infusion reactions can be prevented by premedication. However, severe infusion reactions may require permanent discontinuation of liposomal amphotericin B therapy (see section 4.4).

In two double-blind, comparative studies, the incidence of infusion reactions in patients treated with liposomal amphotericin B was significantly lower than in patients receiving conventional amphotericin B or amphotericin B lipid complex.

Pooled study data from randomised and controlled clinical trials involving over 1,000 patients comparing liposomal amphotericin B with conventional amphotericin B showed that adverse events were significantly less severe and significantly less common in patients treated with liposomal amphotericin B than in patients receiving conventional amphotericin B. Conventional amphotericin B is nephrotoxic to some degree in most patients receiving the drug intravenously. In two double-blind studies, the incidence of nephrotoxicity with liposomal amphotericin B (defined as serum creatinine increase of more than twice baseline) was approximately half that of conventional amphotericin B or amphotericin B lipid complex.
The following adverse reactions based on clinical trial data and post-marketing experience have been observed with liposomal amphotericin B. Frequency is based on analysis of pooled data from clinical trials involving 688 patients treated with liposomal amphotericin B. The frequency of identified adverse reactions based on post-marketing experience is unknown.
Adverse reactions are classified by system organ class (MeDRA) and frequency. Within each frequency grouping, adverse reactions are reported in order of decreasing seriousness.
The frequency of side effects is based on the following categories:
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)

System-Organ class	Very common	Common	Uncommon	Very rare	Not known
Blood and lymphatic system disorders			thrombocytopenia		anaemia
Immune system disorders			anaphylactoid reaction		anaphylactic reactions, hypersensitivity
Metabolism and nutrition disorders	hypokalaemia	hyponatraemia, hypocalcaemia, hypomagnesaemia, hyperglycaemia hyperkalaemia			
Nervous system disorders		headache	convulsions		
Cardiac disorders		tachycardia			cardiac arrest, arrhythmia
Vascular disorders		hypotension, vasodilatation, flushing			
Respiratory, thoracic and mediastinal disorders		dyspnoea	bronchospasm		
Gastrointestinal disorders	nausea, vomiting	diarrhoea, abdominal pain			
Hepatobiliary disorders		abnormal liver function tests, hyperbilirubinaemia, increased alkaline phosphatase			
Skin and		rash			angioneurotic edema

subcutaneous disorders					
Musculoskeletal and connective tissue disorders		back pain			rhabdomyolysis (associated with hypokalaemia), musculoskeletal pain (described as arthralgia or bone pain).
Renal and urinary disorders		increased creatinine and blood urea			renal failure, renal insufficiency
General disorders and administration site conditions	chills, fever	chest pain			

Interference with phosphate assays:
Incorrectly elevated serum phosphate levels may occur when samples from patients receiving liposomal amphotericin B are analyzed with the PHOSm assay (e.g. used in Beckman Coulter analyzers with *Synchron LX20*).
Transient hearing loss, tinnitus, visual disturbances and double vision have been observed in rare cases during therapy with conventional amphotericin B.
After infusions of conventional amphotericin B, the following adverse reactions also occurred with an unknown frequency: increased blood pressure, agranulocytosis, blood clotting disorders, eosinophilia, leukocytosis, leukopenia, encephalopathy, neurological symptoms, peripheral neuropathy, nephrogenic diabetes insipidus, maculopapular exanthema, itching, skin exfoliation, toxic epidermal necrolysis, Stevens-Johnson Syndrome, joint pain, muscle pain, acute liver failure, jaundice.

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 listed in Appendix V*

4.9 Overdose

The toxicity of liposomal amphotericin B due to acute overdose has not been established, however adverse reactions known to be associated with normal doses of liposomal amphotericin B (see section 4.8 Adverse Reactions) are expected.
In case of an overdose, administration must be discontinued immediately. The patient's clinical status including renal and hepatic function, serum electrolytes and haematological status must be carefully monitored. Patients should be managed according to clinical needs. Haemodialysis or peritoneal dialysis does not appear to affect the elimination of liposomal amphotericin B.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals 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 double membranes as soon as they come into contact with aqueous solutions. Due to its lipophilic molecule content, amphotericin B can be stored in the lipid double membrane of the liposomes. Depending on the concentration obtained in body fluids and the sensitivity of the fungus, amphotericin B acts fungistatic or fungicidal.
The drug is thought to work by binding to sterols in the fungal cell membrane, thereby altering the membrane permeability and allowing various small molecules to leak through the membrane. Since mammalian cells also contain sterols, it is assumed that the cell damage caused by amphotericin B in humans and fungi is based on similar mechanisms.
Microbiology:
Amphotericin B, the antifungal component of Amphotericin B liposomal Tillomed, shows *in vitro* a potent activity against a wide range of fungal species, but no or minimal effects on bacteria and viruses.
Samples for fungal cultures and other relevant laboratory tests (serology, histopathology) should be taken prior to therapy to identify causative organisms. Therapy can be initiated before results of cultures and other laboratory tests are known; once the results are available, anti-infective therapy should be adjusted accordingly.
Susceptibility for selected species may vary geographically and with time, and regional information on susceptibility is desirable, particularly in the treatment of severe infections. The information presented in Tables 1 and 2 is intended to provide

guidance on probabilities as to whether or not microorganisms will be susceptible to liposomal amphotericin B. As for all antimicrobial agents, clinical isolates with reduced susceptibility to liposomal amphotericin B have been identified. Susceptibility testing for yeast and spore-forming mould was performed according to the methods of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antimicrobial Susceptibility Testing (AFST-EUCAST, Lass-Flörl et al., Antimicrob Agents Chemother. 2008;52(10):3637-41). See Tables 1 and 2 for *in vitro* susceptibility data (MHK/MIC 90 values).

Table 1. *In vitro* susceptibility of yeast to liposomal amphotericin B

Species	Number of isolates	Range [µg/ml]
Candida species		
C. albicans	59	0.015-0.12
C. glabrata	18	0.5-1
C. parapsilosis	18	0.5-1
C. krusei	19	0.5-2
C. lusitaniae	9	0.06-0.125
C. tropicalis	10	0.25-1
C. guilliermondii	4	0.06-0.12
Other		
Saccharomyces cerevisiae	3	0.03-0.06
Cryptococcus neoformans var. neoformans	10	0.06-0.12
Cryptococcus neoformans var. gattii	3	0.03-0.06
Trichosporon inkin	3	0.03-0.06
Trichosporon asahii	4	0.01-0.03
Geotrichum candidum	4	0.06-0.25

Table 2. *In vitro* susceptibility of moulds to liposomal amphotericin B

Species	Number of isolates	Range [µg/ml]
Aspergillus species		
A. fumigatus	29	0.5-2
A. terreus	34	2-4
A. flavus	21	1-4
A. niger	13	1-2
Zygomycetes		
Rhizomucor species	17	0.3-0.125
Absidia corymbifera	4	0.125-1
Absidia species	17	0.5-2
Rhizopus microsporus var. oligosporus	3	0.03-0.25
Rhizopus oryzae	6	1-4
Rhizopus species	12	1-4

Mucor hiemalis	3	0.03-0.5
Mucor species	11	0.03-0.5
Cunninghamella species	4	0.5-4
Other		
Scedosporium prolificans	2	>8
Scedosporium apiospermum	3	1-2
Penicillium marneffei	2	0.03-0.25
Penicillium species	2	0.5-1
Fusarium solani	2	4-8
Fusarium oxysporum	2	0.03-0.5
Sporothrix schenckii	2	1-2
Curvularia lunata	2	0.125-0.5
Bipolaris australiensis	2	0.01-0.06
Rhinocladiella aquaspersa	2	0.5-1

Liposomal amphotericin B has demonstrated efficacy in animal studies in visceral leishmaniasis (caused by *Leishmania infantum* and *Leishmania donovani*). Mice infected with *Leishmania infantum* were treated with liposomal amphotericin B 3 mg / kg in 3 to 7 doses. All dosing regimens worked faster than sodium antimony gluconate in mice and did not show any toxicity. In mice infected with *Leishmania donovani*, liposomal amphotericin B was 5 times more effective and 25 times less toxic than conventional amphotericin B.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for amphotericin B and are listed here: <https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx>

Clinical efficacy and safety

The effectiveness of liposomal amphotericin B has been established in a number of clinical studies in the treatment of systemic fungal infections, in the treatment of fever of unknown origin in neutropenic patients and in the treatment of visceral leishmaniasis. These studies include comparative randomized trials of liposomal amphotericin B versus conventional amphotericin B with confirmed Aspergillus and Candida infections, in which the effectiveness of both drugs was comparable. In both adults and paediatric patients with a neutropenic fever and suspected fungal infection, the results of a randomized, double-blind clinical study have shown that liposomal amphotericin B administered at 3 mg/kg/day is as effective as conventional amphotericin B. The effectiveness of liposomal amphotericin B in the treatment of visceral leishmaniasis was clearly shown in a large population of immune-competent and immunocompromised patients.

Invasive filamentous fungal infections (IFFIs), including *Aspergillus spp*.: The efficacy of liposomal amphotericin B for the primary treatment of confirmed or probable IFFI was demonstrated in a large-scale, prospective, randomised, multicentre study (AmBiLoad Study) in immunocompromised, mainly neutropenic adults and children (> 30 days). The patients were observed for 12 weeks. A standard dosage with 3 mg/kg/day (n=107) was compared with a loading dose regime of 10 mg/kg/day (n=94) during the first 14 treatment days. The response rate in the modified intent-to-treat analysis set was 50% in patients with standard dosage and 46% with the loading-dose regimen. The differences were not statistically significant. The median time to resolution of fever was similar at the standard dosage and the loading dose regimen (6 and 5 days, respectively). Twelve weeks after the first liposomal amphotericin B administration, the survival rate was 72% with standard dosage and 59% in the loading-dose regimen, a difference that was not statistically significant.

Invasive candidiasis: In a randomised, double-blind, multinational non-inferiority study in adults and children, liposomal amphotericin B (3 mg/kg/day) as a primary treatment of candidaemia or invasive candidiasis was as effective as micafungin (100 mg/day [body weight > 40 kg] or 2 mg/kg/day [body weight ≤ 40 kg]). Liposomal amphotericin B and micafungin were administered for a median duration of 15 days. The response rate was 89.5% (170/190) in the liposomal amphotericin B group and 89.6% (181/202) in the micafungin group (per protocol analysis set) (Kuse et al., Lancet 2007; 369:1519-27). The paediatric sub-study, including the patients from birth, including premature babies showed a numerically higher response rate in patients of all ages treated with liposomal amphotericin B, except premature babies. The response rate was 88.1% (37/42) for liposomal amphotericin B and 85.4% (35/41) for Micafungin (per Protocol Analysis Set) (Queiroz-Zelles et al., The Pediatric Infectious Disease Journal 2008; 27 (9): 1-7)

Invasive mucormycosis (zygomycosis): There are no large-scale, randomized clinical studies in the field of mucormycosis. In a retrospective study over a period of 15 years, 59 hematological patients with confirmed or suspected mucormycosis (zygomycosis) were included. Therapy was successful in 18 patients (37%): 9 out of 39 patients receiving conventional amphotericin B (23%) and 7 out of 12 patients receiving liposomal amphotericin B (58%) responded to therapy (Pagano et al.,

Haematologica. 2004;89(2):207-14). The Working Group on Zygomycosis of the European Confederation of Medical Mycology (ECMM) has prospectively collected cases from patients with zygomycosis. 130 patients received liposomal amphotericin B either alone or in combination as first-line therapy. In patients who received liposomal amphotericin B as the only antifungal medicine and 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). The survival rate was 68% (Skiada et al; Clin Microbiol Infect 2011; 17 (12): 1859-67).
In a pilot study involving 20 patients, liposomal amphotericin B (doses ≥ 5 mg/kg) alone was compared with liposomal amphotericin B plus deferasirox. The overall success rate (survival, clinically stable, radiological improvement) was 67% (6 out of 9 patients) after 30 days and 56% (5 out of 9 patients) after 90 days in the group, which received liposomal amphotericin B alone, each compared to 18 % (2 out of 11 patients) after 30 and 90 days with liposomal amphotericin B plus deferasirox (Spellberg et al; j antimicrob chemother 2012; 67: 715-22).
In a prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B for the initial treatment of mucormycosis, the median duration of treatment of patients receiving 10 mg/kg/day was 13.5 days (range 0-28 days). The primary end point was the success of treatment in week 4 or at the end of treatment (If earlier). Twelve (36%) of 33 evaluable patients responded (18% full remission [Cr; Complete Response], 18% partial remission [Pr; partial response]). The response rate increased to 45% in week 12. The survival rate was 62% in week 12 and 47% in week 24 (Lanternier et al; j Antimicrob Chemother 2015; 70 (11): 3116-23).

5.2 Pharmacokinetic properties

The pharmacokinetic profile of liposomal amphotericin B, based on total plasma concentrations of amphotericin B, was determined in oncology patients with febrile neutropenia and in bone marrow transplant patients who each received 1 hour infusions of 1 - 7.5 mg/kg/day liposomal amphotericin B for 3 to 20 days received. The pharmacokinetic profile of liposomal amphotericin B differs significantly from what is reported in the literature for conventional amphotericin B dosage forms: Both plasma concentration (C_{max}) and exposure (AUC_{0-24}) were higher after administration of liposomal amphotericin B than after administration of conventional amphotericin B. The pharmacokinetic parameters of liposomal amphotericin B after administration of the first and last dose (mean ± standard deviation) were within the following ranges:
C_{max} 7.3µg/ml (±3.8) to 83.7µg/ml (±43.0)
Half-life ($T_{1/2}$) 6.3 h (±2.0) to 10.7 h (±6.4)
AUC_{0-24} 27 µg.hr/ml (±14) to 555 µg.hr/ml (±311)
Clearance (Cl) 11 ml/h/kg (±6) to 51 ml/h/kg (±44)
Volume of distribution 0.10 l/kg (±0.07) to 0.44 l/kg (±0.27)

The minimum and maximum pharmacokinetic values have not necessarily been determined in relation to the respective minimum and maximum doses. After administration of liposomal amphotericin B, the state of equilibrium was rapidly (usually after 4 days of therapy) established (steady state) reached.
The pharmacokinetics of liposomal amphotericin B after administration of the first dose do not appear linear, which means that the serum concentrations of liposomal amphotericin B are disproportionate to the increased dose. This non-proportional dose-response relationship is believed to be due to saturation of reticuloendothelial liposomal amphotericin B clearance. There was no significant accumulation of drug in plasma after repeated administration of 1 to 7.5 mg/kg/day. The volume of distribution at day 1 and at steady state suggests that liposomal amphotericin B is extensively distributed to tissues. The terminal half-life ($t_{½}\beta$) of liposomal amphotericin B after repeated dosing was approximately 7 hours. Values were measured in a range of six to ten hours. Excretion of liposomal amphotericin B has not been studied. The metabolic pathways of amphotericin B and liposomal amphotericin B are unknown.
Based on the liposome size, it is assumed that liposomal amphotericin B does not undergo glomerular filtration nor is excreted renally, thus avoiding interaction of amphotericin B with the cells of the distal tubules and reducing the risk of nephrotoxicity seen with conventional amphotericin B dosage forms.
Renal impairment
The effect of renal impairment on the pharmacokinetics of liposomal amphotericin B has not been explicitly studied. Based on the available data, it can be assumed that no dose adjustment is necessary in patients undergoing haemodialysis or haemofiltration procedures. However, if possible, Amphotericin B liposomal Tillomed should not be administered during the actual procedure.

5.3 Preclinical safety data

In subchronic toxicity studies in dogs (one month), rabbits (one month) and rats (three months) at doses equal to or, in some species, lower than the clinical therapeutic doses of 1 to 3 mg/kg/day, liposomal amphotericin B toxicity was directed towards the liver and kidneys – both of which are also target organs of amphotericin B toxicity.
Liposomal amphotericin B has been shown to be non-mutagenic in bacterial and mammalian systems.
No carcinogenicity studies have been performed with liposomal amphotericin B.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrogenated soy phosphatidylcholine
Cholesterol
Distearoylphosphatidylglycerol
All-*rac*-α-Tocopherol
Sucrose
Disodium succinate hexahydrate
Sodium hydroxide (E524) (for pH adjustment)
Hydrochloric acid, concentrated (37%) (for pH adjustment)

6.2 Incompatibilities

Amphotericin B liposomal Tillomed 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

5 years

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 Tillomedhas 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	4days	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	48hours	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	24 hours
Dextrose 100 mg/mL (10%) solution for	1:2	2.0	48 hours	

infusion	1:20	0.2	48 hours	
Dextrose 200 mg/mL (20%) solution for infusion	1:2	2.0	48 hours	

6.4 Special precautions for storage

Do not store above 25^0 C.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amphotericin B liposomal Tillomed is presented in 20 ml sterile, clear Type I glass vials. The closure consists of a dark grey omniflex 3G coated bromobutyl rubber stopper and aluminium ring flip off seal fitted with a removable blue color un-embossed 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

6.6 Special precautions for disposal

Please read this entire section carefully before starting the preparation.

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

Care should be taken to avoid mixing these products as their dosages vary

Amphotericin B liposomal Tillomed must be reconstituted with sterile water for injections (without antibacterial agents) and diluted in glucose 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) solution for infusion only.

Amphotericin B liposomal Tillomed is not compatible with sodium chloride solution; never dissolve or dilute with sodium chloride solution or administer through an intravenous line, previously used for sodium chloride, unless this was previously rinsed with a glucose 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) solution for infusion. If this is not practicable, Amphotericin B liposomal Tillomed should be administered through a separate line.

Amphotericin B liposomal Tillomed should NOT be mixed with any other drugs or electrolytes. Use aseptic technique during all work steps, since neither Amphotericin B liposomal Tillomed nor the specified solutions for dissolving and diluting contain preservatives.

After reconstitution, pH (between 5.0 and 6.0) and osmolality (between 200 mOsmol/kg to 400 mOsmol/kg).

The ready-to-use Amphotericin B liposomal Tillomed dispersion for infusion is prepared as follows:

1. Inject 12 ml of sterile water for injections into each Amphotericin B liposomal Tillomed vial to obtain a solution containing (total volume 12.5 ml) 4 mg/ ml amphotericin B.

2. IMMEDIATELY after adding the water, SHAKE THE BOTTLE(S) STRONGLY FOR AT LEAST 30 SECONDS to fully disperse the Amphotericin B liposomal Tillomed. After reconstitution with water for injection, the concentrate is a translucent, yellow dispersion. Visually inspect the vial for particulate matter and shake until complete dispersion is achieved but not more than 120 seconds. The dispersion should not be used if there are signs of particle precipitation.

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 (see Table 4).

5. Withdraw the desired volume of reconstituted Amphotericin B liposomal Tillomed into a sterile syringe and transfer into a sterile container with the required amount of glucose 50 mg/mL (5%), 100mg/mL (10%) or 200mg/mL (20%) solution for infusion using the 5 µm filter provided.

An integrated membrane filter can be used for intravenous infusion of Amphotericin B liposomal Tillomed. However, the average pore diameter of the filter should be at least 1.0 µm.

Table 4: Example of the preparation of Amphotericin B liposomal Tillomed dispersion for infusion at a dose of 3 mg/kg/day in glucose 50 mg/mL (5%) solution for infusion.

Body Weight (kg)	Number of vials required	Amount Liposomal amphotericin B (mg) to be withdrawn for further dilution	Volume of reconstituted Liposomal amphotericin B (ml)*	Prepare a 0.2 mg/ml Concentration (1 in 20 dilution)		Prepare a 2.0mg/ml concentration (1 in 2 dilution)	
				Volume required 50 mg/mL (5%) glucose (ml)	Total volume (ml; Liposomal amphotericin B plus 50 mg/mL (5%) glucose)	Volume required 50 mg/mL (5%) glucose (ml)	Total volume (ml; Liposomal amphotericin B plus 50 mg/mL (5%) glucose)
10	1	30	7.5	142.5	150	7.5	15
25	2	75	18.75	356.25	375	18.75	37.5
40	3	120	30	570	600	30	60
55	4	165	41.25	783.75	825	41.25	82.5
70	5	210	52.5	997.5	1050	52.5	105
85	6	255	63.75	1211.25	1275	63.75	127.5

* Each vial of Amphotericin B liposomal Tillomed (50 mg) is reconstituted with 12 ml of Water for Injection to give a concentration of 4 mg/ml of amphotericin B.

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.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Mittelstraße 5/5a
Schönefeld
12529
Germany

8 MARKETING AUTHORISATION NUMBER

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Date of first authorisation: 12th September 2025

10 DATE OF REVISION OF THE TEXT