APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TERISOM (intravenous infusion 50 mg / vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg amphotericin (50 000 units) encapsulated in liposomes.
After reconstitution, the concentrate contains 4 mg / mL amphotericin.
TERISOM contains 900 mg sucrose per vial.
TERISOM contains 27 mg sodium succinate dibasic per vial.
For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Sterile, powder for dispersion for infusion.
Yellow lyophilised cake or powder, free of visible evidence of contamination.
Reconstituted solution: Yellow coloured suspension free from visible foreign particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

TERISOM is indicated for:

- Empirical treatment of presumed fungal infection in febrile neutropaenic adults and children unresponsive to anti-bacterial treatment.
- The treatment of severe systemic and/or deep mycoses in adults and children in whom toxicity (particularly nephrotoxicity) precludes the use of conventional systemic amphotericin B, or in patients who are resistant to conventional amphotericin B. Fungal infections successfully treated with amphotericin B include: disseminated candidiasis, aspergillosis, mucormycosis, chronic mycetoma and cryptococcal meningitis.
- Cryptococcal meningitis in HIV-infected patients. This medicine should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.
- Primary therapy of *visceral leishmaniasis* in immunocompetent adults and children and immunocompromised adults (e.g. HIV positive).

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4.2 Posology and Method of Administration

Posology

Adults

The recommended dosage of **TERISOM** for each indication is provided in the table below:

Table 1:

Indication	**Dose in mg/kg/day**
Empirical therapy	3 mg
Systemic fungal infections: - Aspergillus* - Candida - Cryptococcus	3 mg – 5 mg
Cryptococcal meningitis in HIV infected patients	6 mg
Visceral Leishmaniasis: - Immuno-competent patients - Immuno-compromised patients	3 mg on days 1 - 5, day 14 and day 21 4 mg on days 1 - 5, day 10, day 17, day 24, day 31and day 38

*A large randomised controlled study of amphotericin B as in **TERISOM** reported that a dose of 3 mg/kg/day was optimal for invasive pulmonary aspergillosis.

Elderly Population:

No alteration in dose or frequency of dosing is required.

Renal Impairment:

Amphotericin B as in **TERISOM** has been successfully administered to patients with pre-existing renal impairment at doses of 1- 5 mg/kg/day in reported studies and no adjustment in dose or frequency of administration was required.

Paediatric Population:

Amphotericin B as in **TERISOM** has been studied in paediatric patients aged one month to 18 years old. Dosage should be calculated on the same per Kg body weight basis as for adults.

The safety and efficacy of amphotericin B as in **TERISOM** has not been established in infants under one month old.

Method of administration

TERISOM should be administered by intravenous infusion over a 30 - 60 minute period. For doses greater than 5 mg/kg/day, intravenous infusion over a 2 hour period is recommended (see Section 4.4). The recommended concentration for intravenous infusion is 0,20 mg/mL to 2,00 mg/mL amphotericin B as **TERISOM** (see section 6.6).

4.3 Contraindications

- **TERISOM** is contraindicated in patients who have shown hypersensitivity to amphotericin B or any of its constituents unless, in the opinion of the medical practitioner, the condition requiring treatment is life-threatening and amenable only to **TERISOM** therapy (see Section 6.1).
- Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

Anaphylaxis and anaphylactoid reactions

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

Infusion-related reactions

Severe infusion-related reactions can occur during administration of **TERISOM** (See section 4.8). Consideration of precautionary measures for the prevention or treatment of these reactions should be given to patients who receive **TERISOM** therapy. Slower infusion rates (over two hours) or routine doses of diphenhydramine, paracetamol, pethidine, and/or hydrocortisone have been reported as successful in their prevention or treatment.

Renal toxicity

Liposomal amphotericin B as in **TERISOM** has been reported to be substantially less toxic than conventional amphotericin B, particularly with respect to nephrotoxicity; however, renal adverse reactions may still occur.

In reported studies comparing amphotericin B as in **TERISOM**, 3 mg/kg daily with higher doses (5, 6 or 10 mg/kg daily), it was reported that the incidence rates of increased serum creatinine, hypokalaemia and hypomagnesaemia have been notably higher in the high dose groups.

Prolonged therapy

Adverse events may occur and caution should be exercised when prolonged therapy is required. Regular laboratory evaluation of renal, hepatic and haematopoietic function

should be performed. This is particularly important in patients receiving concomitant nephrotoxic medications (See section 4.5). Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of **TERISOM** infusion administration. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reductions, treatment interruption or discontinuation.

Acute 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 these infusions are separated by as long a period as possible and pulmonary function should be monitored.

In the treatment of diabetic patients:
Excipients
Sucrose: It should be noted that **TERISOM** contains approximately 900 mg of sucrose in each vial.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Sodium: **TERISOM** contains 27 mg sodium succinate dibasic per vial.

4.5 Interaction with other medicines and other forms of interaction
No specific interaction studies have been reported with amphotericin B as in **TERISOM**. However, the following medicines are known to interact with amphotericin B and may interact with **TERISOM**.

Nephrotoxic medications:
Concurrent administration of amphotericin B as in **TERISOM** with other nephrotoxic medicines, for example cyclosporine, aminoglycosides and pentamidine, may enhance the potential for medicine-induced renal toxicity. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, **TERISOM** has relatively less nephrotoxicity.

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

Corticosteroids, corticotrophin (ACTH) and diuretics
Concurrent use of corticosteroids, corticotrophin (ACTH) and diuretics (loop and thiazide) may potentiate hypokalaemia.

Digitalis glycosides

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TERISOM infusion-induced hypokalaemia may potentiate digitalis toxicity.

Skeletal muscle relaxants
TERISOM-induced hypokalaemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine).

Antifungals
No evidence of benefit from the use of flucytosine with amphotericin B as in **TERISOM** has been reported. Whilst synergy between amphotericin and flucytosine has been reported. Concurrent use with flucytosine may increase the toxicity of flycytosine by possible increasing its cellular uptake and/or impairing its renal excretion.

Antineoplastic medicines
Concurrent use of antineoplastic medicines may enhance the potential for renal toxicity, bronchospasm and hypotension. Antineoplastic medicines should be given concomitantly with caution.

Leucocyte 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 that these infusions are separated by as long a period as possible and pulmonary function should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of **TERISOM** 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 foetus, but the number of cases reported is insufficient to draw any conclusions on the safety of **TERISOM** in pregnancy.

Breast-feeding
It is unknown whether **TERISOM** is excreted in human breast milk. The safety of taking **TERISOM** during breastfeeding has not been established.

Fertility
Reported animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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 reported.

Some of the undesirable effects of **TERISOM** presented below may impact the ability to drive and use machines.

4.8 Undesirable Effects

Summary of adverse reactions:

Fever and chills/rigors are the most frequent infusion-related reactions expected to occur during amphotericin B as in **TERISOM** administration. Less frequent infusion-related reactions may consist of one or more of the following symptoms: back pain, chest tightness or pain, dyspnoea, bronchospasm, flushing, tachycardia, and hypotension. These resolved rapidly on stopping the infusion and may not occur with every subsequent dose or when slower infusion rates (over 2 hours) are used.

In addition, infusion-related reactions may also be prevented by the use of premedication. However, severe infusion-related reactions may necessitate the permanent discontinuation of **TERISOM**.

The following adverse reactions have reported with amphotericin B as in **TERISOM**, based on clinical trial data and post-marketing experience. The frequency is based on analysis from pooled clinical studies of amphotericin B 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 and are sorted by frequency.

Table 2

System organ class	Frequent	Less frequent	Frequency not known
Blood and lymphatic system disorders		Thrombocytopenia	Anaemia
Immune system disorders		Anaphylactoid reactions	Anaphylactic reactions, hypersensitivity

Metabolism and nutritional disorders	Hypokalaemia, Hypomagnese-mia,hypocal-caemia, hyperglycaemia, hyponatraemia	-	-
Nervous system disorders	Headache	Convulsion	-
Cardiac disorders	Tachycardia	-	Cardiac arrest, arrhythmia
Vascular disorders	Vasodilation, flushing, hypotension	-	-
Respiratory thoracic and mediastinal disorder	Dyspnoea,	Bronchospasm	-
Gastro-intestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain	-	-
Hepatobiliary disorders	Liver function test abnormal, hyperbilirubi-naemia, alkaline phosphatase increased.	-	-
Renal and urinary disorders	Increased creatinine, blood urea increased	-	Renal failure, renal insufficiency
Skin and subcutaneous disorders	Rash	-	Angioneurotic oedema

Musculoskeletal and connective tissue disorders	Back pain	-	Rhabdomyo-losis (associated with hypokalaemia),musculoskeletal pain (described as arthralgia or bone pain)
General disorders and administration site conditions	Pyrexia, rigors, chest pain	-	-

Description of selected adverse reactions

Infusion-related reactions

It has been reported that, amphotericin B as in **TERISOM** 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.

Renal toxicity

Nephrotoxicity occurs to some degree with conventional amphotericin B in most patients receiving the product intravenously. In reported study, the incidence of nephrotoxicity with amphotericin B (as measured by serum creatinine increase greater than 2,0 times baseline measurement), was approximately half that for conventional amphotericin B. In another reported study, the incidence of nephrotoxicity with amphotericin B (as measured by serum creatinine increase greater than 2,0 times baseline measurement) was approximately half that for amphotericin B lipid complex.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The toxicity of **TERISOM** due to overdose has not been defined. If overdose should occur, cease administration immediately. Carefully monitor clinical status including renal and hepatic function, serum electrolytes and haematologic status. Haemodialysis or peritoneal dialysis does not appear to enhance the elimination of **TERISOM.**

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.2 Antimicrobials: Fungicides
Pharmacotherapeutic group: Antimycotics for systemic use, antibiotics; ATC code: J02AA01.

Mechanism of action

Amphotericin B is a macrocyclic, polyene antifungal antibiotic produced by *Streptomyces nodosus.* Liposomes are closed, spherical vesicles formed from a variety of amphiphilic substances such as phospholipids. Phospholipids arrange themselves into membrane bilayers when exposed to aqueous solutions.

The lipophilic moiety of amphotericin allows the medicine to be integrated into the lipid bilayer of the liposomes. Amphotericin B is fungistatic or fungicidal depending on the concentration attained in body fluids and the susceptibility of the fungus. The medicine probably acts 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.

Amphotericin B is active *in vitro* against many species of fungi. Most strains of *Histoplasma capsulatum, coccidiodes immitis, Candida spp, Blastomyces dermatitides, Rhodotorula, Cryptococcus neoformans, Sporothrix schenkii, Mucor mucedo and Aspergillus fumigatus*, are inhibited by concentrations of amphotericin B ranging from 0,03 to 1,0 µg/ml *in vitro*. Amphotericin B has minimal or no effect on bacteria and viruses.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of amphotericin B, based upon total plasma concentrations of amphotericin B, has been reported in cancer patients with febrile neutropenia and bone marrow transplant patients who received 1 - 2 hour infusions of 1,0 to 7,5 mg/kg/day amphotericin B for 3 to 20 days.

After the first and last dose and at steady state the pharmacokinetic parameters of amphotericin B (mean ± standard deviation) ranged from:

Table 3

C_{max}:	7,3 µg/mL (± 3,8) to 83,7 µg/mL (± 43,0)
$T_{½}$:	6,3 hr (± 2,0) to 10,7 hr (± 6,4)
AUC_{0-24}:	27 µg,hr/mL (± 14) to 555 µg,hr/mL (± 311)
Clearance (Cl):	11 mL/hr/kg (± 6) to 51 ml/hr/kg (± 44)

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Volume of distribution (Vss):	0,10 l/kg (± 0,07) to 0,44 l/kg (± 0,27)

Minimum and maximum pharmacokinetic values do not necessarily come from the lowest and highest doses, respectively.

Absorption
Amphotericin B pharmacokinetics following the first dose appear non-linear such that serum amphotericin B concentrations are greater than proportional with increasing dose. This non-proportional dose response is believed to be due to saturation of reticuloendothelial amphotericin B clearance. There was no significant drug accumulation in the plasma following repeated administration of 1 to 7,5 mg/kg/day.

Distribution
Volume of distribution on day 1 and at steady state suggests that there is extensive tissue distribution of liposomal infusion.

Elimination
After repeated administration of amphotericin B the terminal elimination half-life (t½β) for amphotericin B was approximately 7 hours. This long terminal elimination half-life is believed to be due to slow redistribution of amphotericin B. The excretion of amphotericin B has not been reported. The metabolic pathways of amphotericin B ~~and amphotericin B~~ are not known. Due to the size of the liposomes there is no glomerular filtration and renal elimination of amphotericin B.

Special populations
Renal Impairment
The effect of renal impairment on the pharmacokinetics of amphotericin B has not been reported. Data suggest that no dose adjustment is required in patients undergoing hemodialysis or filtration procedures, however, amphotericin B 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.

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Breakpoints
EUCAST breakpoints for amphotericin B (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).*

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Distearoylphosphatidyl glycerol, Hydrogenated soya phosphatidylcholine, Cholesterol NF, DL-Alpha-Tocopherol USP, Sucrose NF, Sodium succinate dibasic hexahydrate.

6.2 Incompatibilities

Terisom is incompatible with saline solutions and may not be mixed with other medicinal products or electrolytes (see section 4.2).
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 Months
As **TERISOM** does not contain any bacteriostatic agent, from a microbiological point of view, the reconstituted ordiluted 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 **TERISOM** 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

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DO NOT STORE partially used vials for future patient use.

Shelf-life after dilution with Dextrose:
Table 4

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

TERISOM 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

TERISOM is presented in 15 ml, 20 ml or 30 ml sterile, Type I glass vials. The closure consists of a grey butyl rubberstopper 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

TERISOM is not equivalent to other amphotericin products (see section 4.2).

TERISOM must only 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) inthe solution, may cause precipitation of **TERISOM**.

TERISOM 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, **TERISOM** should be administered through a separate line.

Do NOT mix **TERISOM** with other medicinal products or electrolytes.

Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in **TERISOM**, or in the materials specified for reconstitution

and dilution.

TERISOM must be reconstituted by suitably trained staff.

Vials of **TERISOM** containing 50 mg of amphotericin are prepared as follows:

1. Add 12 ml of Sterile Water for Injection to each **TERISOM** vial, to yield a preparation containing 4 mg/mlamphotericin.
2. IMMEDIATELY after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 seconds to completelydisperse the **TERISOM**. After reconstitution the concentrate is a translucent, yellow dispersion. Visually inspectthe vial for particulate matter and continue shaking until complete dispersion is obtained. Do not use if there isany evidence of precipitation of foreign matter.
3. Calculate the amount of reconstituted (4 mg/ml) **TERISOM** to be further diluted (see table below).
4. The infusion solution is obtained by dilution of the reconstituted **TERISOM** with between one (1) and nineteen(19) parts dextrose solution (5%, 10% or 20%) for infusion by volume, to give a final concentration in therecommended range of 2.00 mg/ml to 0.20 mg/ml amphotericin as **TERISOM** (see table below).
5. Withdraw the calculated volume of reconstituted **TERISOM** into a sterile syringe. Using the 5 micron filterprovided, instill the **TERISOM** 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 **TERISOM**. However, the mean pore diameter of the filter should not be less than 1.0 micron.

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

Table 5

Weight (kg)	Number of vials	Amount **TERISOM** (mg) to be withdrawn for further dilution	Volume of reconstituted **TERISOM** (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; **TERISOM** plus 5% dextrose)	Volume of 5% dextrose needed (mL)	Total volume (mL; **TERISOM** 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

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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 **TERISOM** (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

Ranbaxy Pharmaceuticals (Pty) Ltd
14 Lautre Road, Stomill, Ext 1
Roodepoort, 1724

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION

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