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

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

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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)

56/20.2.2/1125

9. DATE OF FIRST AUTHORISATION

20 June 2023

10. DATE OF REVISION OF THE TEXT

GOEDGEKEURDE PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S4

1. NAAM VAN DIE MEDISYNE

TERISOM (intraveneuse infusie) 50 mg / flessie

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke flessie bevat 50 mg amfoterisien (50 000 eenhede) geënkapsuleer in liposome.

Na hersamestelling bevat die konsentraat 4 mg / mL amfoterisien.

TERISOM bevat 900 mg sukrose per flessie.

TERISOM bevat 27 mg dibasiese natriumsuksinaat per flessie.

Vir die volledige lys van onaktiewe bestanddele, sien **afdeling 6.1**

3. FARMASEUTIESE VORM

Steriele, poeier vir verspreiding vir infusie.

Geel gevriesdroogde koekie of poeier, vry van sigbare bewys van kontaminasie.

Hersaamgestelde oplossing: Geelkleurige suspensie vry van sigbare vreemde deeltjies.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

TERISOM word aangedui vir:

- Empiriese behandeling van vermoedelike fungusinfeksies in koorsige neutropeniese volwassenes en kinders wat nie op anti-bakteriële behandeling reageer nie.
- Die behandeling van ernstige sistemiese en/of diep swambesmetting in volwassenes en kinders by wie toksisiteit (veral nefrotoksisiteit) die gebruik van konvensionele sistemiese amfoterisien-B uitsluit, of in pasiënte wat weerstandig is teen konvensionele amfoterisien-B.

  Fungusinfeksies wat suksesvol met amfoterisien-B behandel word, sluit in: verspreide kandidiase, aspergillose, mukormikose, chroniese misetoma en kriptokokkale meningitis.
- Kriptokokkale meningitis in MIV-geïnfekteerde pasiënte. Hierdie medisyne moet nie gebruik word om die algemene kliniese onsigbare vorme van fungussiekte wat slegs positiewe vel of serologiese toetse toon, te behandel nie.
- Primêre terapie van *viserale leishmaniase* in immuunbevoegde volwassenes en kinders en immuungekompromitteerde volwassenes (bv. MIV-positief).

4.2 Posologie en Metode van Toediening

Posologie

Volwassenes

Die aanbevole dosis van **TERISOM** vir elke indikasie word in die tabel hieronder voorsien:

Tabel 1:

Indikasie	**Dosis in mg/kg/dag**
Empiriese terapie	3 mg
Sistemiese fungusinfeksies: - Aspergillus* - Candida - Cryptococcus	3 mg – 5 mg
Kriptokokkale meningitis in MIV-geïnfekteerde pasiënte	6 mg
Viserale Leishmaniasis: - Immuunbevoegde pasiënte - Immuun-kompromitteerde pasiënte	3 mg op dag 1 - 5, dag 14 en dag 21 4 mg op dag 1 - 5, dag 10, dag 17, dag 24, dag 31 en dag 38

*'n Groot gerandomiseerde gekontrolleerde studie van Amfoterisien-B, soos in **TERISOM,** het aangetoon dat 'n dosis van 3 mg/kg/dag optimaal was vir indringende pulmonêre aspergillose.

Bejaarde Populasie:

Geen verandering aan dosis of frekwensie van dosering word benodig nie.

Nierinkorting:

Amfoterisien-B, soos in **TERISOM,** is in aangemelde studies suksesvol toegedien aan pasiënte met voorafbestaande nierinkorting teen dosisse van 1- 5 mg/kg/dag en geen dosisaanpassing of frekwensie van toediening is benodig nie.

Pediatriese Populasie:

Amfoterisien-B, soos in **TERISOM,** is in pediatriese pasiënte van die ouderdom een maand tot 18-jaar oud bestudeer. Dosis moet bereken word op dieselfde massa-basis per Kg liggaamsgewig soos vir volwassenes.

Die veiligheid en doeltreffendheid van amfoterisien-B, soos in **TERISOM,** is nie vasgestel in suigelinge onder die ouderdom van een maand nie.

Metode van toediening

TERISOM moet deur intraveneuse infusie oor ‘n periode van 30-60 minute toegedien word. Vir dosisse groter as 5 mg/kg/dag, word intraveneuse infusie oor ‘n 2-uur periode aanbeveel (sien afdeling 4.4). Die aanbevole konsentrasie vir intraveneuse infusie is 0,20 mg/mL tot 2,00 mg/mL amfoterisien-B, soos **TERISOM** (sien afdeling 6.6).

4.3 Kontraindikasies

- **TERISOM** is teenaangedui in pasiënte wat hipersensitiwiteit teen amfoterisien-B of enige van die bestanddele aangetoon het, tensy die mediese praktisyn van opinie is dat die toestand wat behandel moet word, lewensbedreigend is en slegs vatbaar is vir **TERISOM-**terapie (sien afdeling 6.1).
- Veiligheid in swangerskap en laktasie is nie vasgestel nie.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Anafilakse en anafilaktoïede reaksies

Anafilakse en anafilaktoïede reaksies is aangemeld in assosiasie met amfoterisien-B infusie, soos in **TERISOM**. As ‘n ernstige anafilaktiese/anafilaktoïede reaksie voorkom, moet die infusie onmiddellik gestaak word en die pasiënt moet geen verdere infusie van **TERISOM** ontvang nie.

Infusie-verwante reaksies

Ernstige infusie-verwante reaksies kan voorkom tydens toediening van **TERISOM** (sien afdeling 4.8). Oorweging van voorsorgmaatreëls vir die voorkoming of behandeling van hierdie reaksies moet toegepas word by pasiënte wat **TERISOM-**terapie ontvang. Stadiger infusie-tempo (oor twee uur) of normale dosisse van difenhidramien, parasetamol, petidien, en/of hidrokortisoon is aangemeld om suksesvol te wees in hul voorkoming of behandeling.

Nefrotoksisiteit

Liposomale amfoterisien-B, soos in **TERISOM,** is aangemeld om wesentlik minder toksies as konvensionele amfoterisien-B te wees, veral met betrekking tot nefrotoksisiteit; alhoewel ongewenste nierreaksies steeds kan voorkom.

In aangemelde studies waar amfoterisien-B, soos in **TERISOM**, 3 mg/kg daagliks met hoër dosisse (5, 6 of 10 mg/kg daagliks) vergelyk is, is dit aangemeld dat die voorkomskoers van verhoogde serumkreatinien, hipokalemie en hipomagnesemie aansienlik hoër is in die hoër-dosis groepe.

Langdurige terapie

Ongunstige voorvalle kan voorkom en versigtigheid moet toegepas word wanneer langdurige terapie benodig word. Gereëlde laboratorium-evaluaise van nier-, lewer- en hematopoïetiese funksie moet uitgevoer word. Dit is veral belangrik in pasiënte wat

gelyktydige nefrotoksiese medikasie ontvang (sien afdeling 4.5). As gevolg van die risiko van hipokalemie, mag toepaslike kaliumaanvulling nodig wees tydens die verloop van die **TERISOM-**infusie toediening. Indien merkbare kliniese afname in nierfunksie of verergering van ander parameters voorkom, moet oorweging geskenk word aan dosisverlaging, onderbreking of staking van behandeling.

Akute pulmonêre toksisiteit
Akute pulmonêre toksisiteit is aangemeld in pasiënte wat amfoterisien-B (as natrium-deoksicholaat-kompleks) ontvang tydens of kort ná leukosiet-transfusies. Daar word aanbeveel dat hierdie infusies deur ‘n tydperk vir so lank as moontlik tussen mekaar gedoen word en pulmonêre funksie moet gemonitor word.

In die behandeling van diabetiese pasiënte:
Onaktiewe bestanddele
Sukrose: Daar moet kennis geneem word dat **TERISOM** ongeveer 900 mg sukrose in elke flessie bevat.
Pasiënte met seldsame oorerflike probleme van fruktose-onverdraagsaamheid, glukose-galaktose wanabsorpsie of sukrase-isomaltase-tekort, moet nie hierdie medisyne neem nie.
Natrium: **TERISOM** bevat 27 mg dibasiese-natriumsuksinaat per flessie.

4.5 Interaksie met ander medisyne en ander vorme van interaksie

Geen spesifieke interaksie-studies is met amfoterisien-B, soos in **TERISOM,** aangemeld nie. Die volgende medisyne is egter bekend daarvoor om interaksie met amfoterisien-B te hê en kan interaksie met **TERISOM** hê.

Nefrotoksiese medisyne:
Gelyktydie toediening van amfoterisien-B, soos in **TERISOM,** met ander nefrotoksiese medisyne, byvoorbeeld siklosporien, aminoglikosiede en pentamidien, kan die moontlikheid vir medisyne-geïnduseerde nefrotoksisiteit versterk. Alhoewel, in pasiënte wat gelyktydig siklosporien en/of aminoglikosiede ontvang, het **TERISOM** relatief minder nefrotoksisiteit.

Gereëlde monitering van nierfunksie word aanbeveel in pasiënte wat amfoterisien-B saam met enige nefrotoksiese medisyne ontvang.

Kortikosteroïede, kortikotrofien (ACTH) en diuretika
Gelyktydige gebruik van kortikosteroïede, kortikotrofien (ACTH) en diuretika (lus en tiasied) kan hipokalemie versterk.

Digitalisglikosiede

TERISOM infusie-geïnduseerde hipokalemie kan digitalis-toksisiteit versterk.

Skeletspierverslappers
TERISOM-geïnduseerde hipokalemie kan die kurarivorme effek van skeletspierverslappers (bv. tubokurarien) versterk.

Antifungusmiddels
Geen bewys van die voordeel vir die gebruik van flusitosien saam met amfoterisien-B, soos in **TERISOM,** is aangemeld nie. Terwyl 'n sinergie tussen amfoterisien en flusitosien aangemeld is. Gelyktydige gebruik met flusitosien kan die toksisiteit van flusitosien verhoog deur moontlike verhoging van die sellulêre heropname en/of benadeling van die renale uitskeiding.

Antineoplastiese medisyne
Gelyktydige gebruik van antineoplastiese medisyne kan die potensiaal vir nefrotoksisiteit, brongospasma en hipotensie verhoog. Antineoplastiese medisyne moet met versigtigheid gelyktydig toegedien word.

Leukosiet-transfusies
Akute pulmonêre toksisiteit is aangemeld in pasiënte wat amfoterisien-B (as natrium-deoksicholaat-kompleks) tydens of kort ná leukosiet-transfusies ontvang het. Daar word aanbeveel dat hierdie transfusies vir so lang periode as moontlik uitmekaar toegedien word en pulmonêre funksie moet gemonitor word.

4.6 Fertiliteit, swangerskap en laktasie
Swangerskap
Die veiligheid van **TERISOM** in swanger vrouens is nie vasgestel nie.
Sistemiese fungusinfeksies is suksesvol in swanger vrouens met konvensionele amfoterisien-B behandel sonder sigbare effekte op die fetus, maar die aantal aangemelde gevalle is onvoldoende om enige gevolgtrekking oor die veiligheid van **TERISOM** in swangerskap te maak.

Borsvoeding
Dit is onbekend of **TERISOM** in menslike borsmelk uitgeskei word. Die veiligheid om **TERISOM** tydens borsvoeding te neem, is nie vasgestel nie.

Fertiliteit
Aangemelde dierestudies dui nie op direkte of indirekte skadelike effekte met betrekking tot voortplantingstoksisiteit nie.

4.7 Effekte op die vermoë om te bestuur en masjinerie te gebruik

Geen studies op die effekte op die vermoë om te bestuur of masjinerie te gebruik, is aangemeld nie.

Sommige van die ongewenste effekte van **TERISOM,** hieronder aangedui, kan die vermoë om te bestuur of masjinerie te gebruik beïnvloed.

4.8 Ongewenste Effekte

Opsomming van ongunstige reaksies:

Koors en koue/koudheid is die mees algemene infusie-verwante reaksies wat verwag word om voor te kom tydens toediening van amfoterisien-B, soos in **TERISOM.** Minder algemene infusie-verwante reaksies kan bestaan uit een of meer van die volgende simptome: rugpyn, benoude bors of pyn, dispnee, brongospasma, blosing, tagikardie, en hipotensie. Hierdie klaar vinnig op wanneer die infusie gestaak word en mag nie voorkom met elke opeenvolgende dosis nie of wanneer stadiger infusie-tempo (oor 2 uur) gebruik word.

Bykomend kan infusie-verwante reaksies voorkom word deur die gebruik van pre-medikasie. Ernstige infusie-verwante reaksies kan egter die permanente onttrekking van **TERISOM** noodsaak.

Die volgende ongunstige reaksies is aangemeld met amfoterisien-B, soos in **TERISOM**, gebaseer op kliniese proefdata en na-bemarkingservaring. Die voorkoms is gebaseer op analise van saamgevoegde kliniese studies van amfoterisien-B-behandelde pasiënte. Die voorkoms van ongunstige reaksies van na-bemarkingservaring is nie bekend nie.

Ongunstige reaksies word hieronder gelys volgens liggaamsorgaanklas-stelsel en word gesorteer volgens voorkoms.

Tabel 2

Orgaanklas-stelsel	**Dikwels**	**Minder dikwels**	**Voorkoms onbekend**
Bloed- en limfatiese stelselversteurings		Trombositopenie	Anemie
Immuunstelsel-versteurings		Anafilaktoïede reaksies	Anafilaktiese reaksies, hipersensitiwiteit

Metabolisme en voedings-versteurings	Hipokalemie, Hipomagnes-emie,hipo-kalsemie, hiperglukemie, hiponatremie	-	-
Senuweestelsel-versteurings	Hoofpyn	Konvulsie	-
Kardiale versteurings	Tagikardie	-	Hartarres, arritmie
Vaskulêre versteurings	Vasodilatasie, blosing, hipotensie	-	-
Respirato-riese, torakale en mediastinale versteurings	Dispnee	Brongospasma	-
Gastroïntestinale versteurings	Naarheid, braking, diaree, abdominale pyn	-	-
Hepatobiliêre versteurings	Abnormale lewerfunksie-toetse, hiperbilirubin-emie, verhoogde alkaliese fosfatase	-	-
Renale en urinêre versteurings	Verhoogde kreatinien, verhoogde bloedureum	-	Nierversaking, nierontoe-reikendheid
Vel-en subkutane weefsel-versteurings	Uitslag	-	Angio-neurotiese edeem

Muskuloskeletale en bindweefsel-versteurings	Rugpyn	-	Rabdomiolise (geassosieer met hipokalemie), muskulo-skeletale pyn (beskryf as artralgie of beenpyn)
Algemene versteurings en toedienplek-toestande	Pireksie, koudheid, borskaspyn	-	-

Beskrywing van geselekteerde ongunstige reaksies

Infusie-verwante reaksies

Daar is aangemeld dat amfoterisien-B, soos in **TERISOM-**behandelde pasiënte, 'n aansienlik laer voorkoms van infusie-verwante reaksies, vergeleke met pasiënte wat met konvensionele amfoterisien-B of amfoterisien-B lipiedkomleks behandel is, ervaar.

Renale toksisiteit

Nefrotoksisiteit kom tot 'n sekere mate voor met konvesionele amfoterisien-B in meeste pasiënte wat die produk intraveneus ontvang. In 'n aangemelde studie was die voorkoms van nefrotoksisiteit met amfoterisien-B (soos gemeet deur serumkreatinien-verhoging meer as 2,0 keer basislynmeting), ongeveer die helfte as die vir konvensionele amfoterisien-B. In 'n ander aangemelde studie, was die voorkoms van nefrotoksisiteit met amfoterisien-B (soos gemeet deur serumkreatinien-verhoging meer as 2,0 keer basislynmeting) ongeveer die helfte as die vir amfoterisien-B lipiedkompleks.

Aanmelding van ongunstige reaksies

Aanmelding van vermoedelike ongunstige reaksies na goedkeuring van die medisyne is belangrik. Dit verseker voortdurende monitering van die voordeel/risiko balans van die medisyne. Gesondheidsorgvoorsieners word versoek om enige vermoedelike ongunstige reaksies by SAHPRA aan te meld *via* die "6.04 Adverse Drug Reaction Reporting Form", wat aanlyn onder SAHPRA se publikasies beskikbaar is:
https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosis

Die toksisiteit van **TERISOM** as gevolg van oordosis is nie bepaal nie. Indien oordosis sou voorkom, staak toediening onmiddellik. Kliniese status, insluitend renale en hepatiese funksie, serumelektroliete en hematologiese status moet noukeurig gemonitor word. Dit

kom nie voor asof hemodialise of peritoneale dialise die eliminasie van **TERISOM** vermeerder nie**.**

5 FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Kategorie en klas: A 20.2.2 Antimikrobiese middels: Fungisiede
Farmakoterapeutiese groep: Antimikotika vir sistemiese gebruik, antibiotika; ATC-kode: J02AA01.

Meganisme van werking

Amfoterisien-B is ‘n makrosikliese, poliëen antifungus antibiotikum geproduseer deur *Streptomyces nodosus.* Liposome is geslote, sferiese vesikels wat gevorm word van ‘n verskeidenheid van amfifiliese bestanddele soos fosfolipiede. Fosfolipiede rangskik hulleself in tweelagige membrane wanneer aan waterige oplossings blootgestel word.

Die lipofiliese gedeelte van amfoterisien laat toe dat die medisyne geïntegreer kan word in die tweelagige lipied van die liposome. Amfoterisien-B is fungistaties of fungisidies afhangend van die konsentrasie wat bereik word in liggaamsvloeistowwe en die vatbaarheid van die fungus. Die medisyne werk waarskynlik deur binding aan sterole in die fungus se selmembraan met ‘n gevolglike verandering in membraandeurlaatbaarheid, wat lekkasie van ‘n verskeidenheid van klein molekules toelaat. Soogdier-selmembrane bevat ook sterole, en dit word gesuggereer dat die skade wat aan menslike selle en fungusselle veroorsaak word deur amfoterisien-B algemene meganismes mag deel.

Amfoterisien-B is *in vitro* aktief teen baie spesies van fungi. Meeste stamme van *Histoplasma capsulatum, coccidiodes immitis, Candida spp, Blastomyces dermatitides, Rhodotorula, Cryptococcus neoformans, Sporothrix schenkii, Mucor mucedo en Aspergillus fumigatus*, word geïnhibeer deur konsentrasies van amfoterisien-B wat wissel van 0,03 tot 1,0 µg/mL *in vitro*. Amfoterisien-B het minimale of geen effek op bakterieë en viruses nie.

5.2 Farmakokinetiese eienskappe

Die farmakokinetiese profiel van amfoterisien-B, gebaseer op die totale plasmakonsentrasies van amfoterisien-B, is aangemeld in kankerpasiënte met koorsige neutropenie en beenmurgoorplantingspasiënte wat 1-2-uur infusies van 1,0 tot 7,5 mg/kg/dag amfoterisien-B vir 3 tot 20 dae ontvang het.

Na die eerste en laaste dosis en by gelykstaat wissel die farmakokinetiese parameters van amfoterisien-B (gemiddeld ± standaardafwyking) van:

Tabel 3

C_{maks}:	7,3 µg/mL (± 3,8) tot 83,7 µg/mL (± 43,0)

$T_{½}$:	6,3 hr (± 2,0) tot 10,7 hr (± 6,4)
AOK_{0-24}:	27 µg,hr/mL (± 14) tot 555 µg,hr/mL (± 311)
Opruiming (Cl):	11 mL/hr/kg (± 6) tot 51 ml/hr/kg (± 44)
Volume of verspreiding (Vss):	0,10 l/kg (± 0,07) tot 0,44 l/kg (± 0,27)

Minimum en maksimum farmakokinetiese waardes word nie noodwendig van die laagste en hoogste dosisse, respektiewelik, verkry nie.

Absorpsie
Amfoterisien-B farmakokinetika na die eerste dosis blyk om nie-lineêr te wees nie sodat amfoterisien-B konsentrasies groter as proporsioneel met verhoogde dosis is. Daar word gemeen dat hierdie nie-proporsionele dosisrespons as gevolg van versadiging van retikulo-endoteliale amfoterisien-B-opruiming is. Daar was geen beduidende geneesmiddel-akkumulasie in die plasma na herhaaldelike toediening van 1 tot 7,5 mg/kg/dag nie.

Verspreiding
Volume van verspreiding op dag 1 en by gelykstaat suggereer dat daar uitgebreide weefselverspreiding van liposomale infusie is.

Eliminasie
Na herhaalde toediening van amfoterisien-B is die terminale halfleeftyd (t½β) vir amfoterisien-B ongeveer 7 uur. Daar word aangemeen dat hierdie lang terminale eliminasie halfleeftyd as gevolg van stadige herverspreiding van amfoterisien-B is. Die uitskeiding van amfoterisien-B is nie aangemeld nie. Die metaboliese weë van amfoterisien-B is nie bekend nie. As gevolg van die grootte van die liposome is daar geen glomerulêre filtrasie en renale eliminasie van amfoterisien-B nie.

Spesiale populasies
Renale Inkorting
Die effek van renale inkorting op die farmakokinetika van amfoterisien-B is nie aangemeld nie. Data stel voor dat geen dosisaanpassing nodig is in pasiënte wat hemodialise of filtrasie-prosedures ondergaan nie, amfoterisien-B-toediening moet egter vermy word tydens die prosedure.

Farmakokinetiese/farmakodinamiese verwantskap
Meganisme van weerstand

Intrinsieke weerstand, egter selde, kan hoofsaaklik wees as gevolg van afname in ergosterol of ‘n verandering in die teikenlipied, wat lei tot ‘n verlaagde binding van amfoterisien-B aan die selmembraan.

Breekpunte
EUCAST breekpunte vir Amfoterisien B (L-AmB) is nognie vasgestel nie, vatbaarheid vir L-AmB mag egter verskil van die van Amfoterisien B-deoksicholaat.

Amfoterisien-B, die antifunguskomponent van L-AmB, is *in vitro* aktief teen baie spesies van fungi, meeste stamme van *Histoplasma capsulatum*, *Coccidioides immitis*, *Candida* spp, *Blastomyces dermatidis*, *Rhodotorula*, *Cryptococcus neoformans*, *Sporothrix schenkii* en *Aspergillus fumigatus*, *Penicillium marneffi*, en lede van die mukomisete-groep van swamme, insluitend *Mucor mucedo*, *Rhizomucor* en *Rhizopus oryzae*.
Die meerderheid van klinies-belangrike fungus-spesies blyk vatbaar te wees vir amfoterisien-B, alhoewel intrinsieke weerstand selde aangemeld word, byvoorbeeld vir sommige stamme van *S. schenckii*, *C. glabrata, C. krusei, C. tropicalis, C. lusitaniae, C. parapsilosis* en *Aspergillus terreus.*
Daar is aangedui dat L-AmB effektief is in diere-modelle van viserale leishmaniase (veroorsaak deur *Leishmania infantum* en *Leishmania donovani).*

6 FARMASEUTIESE BESONDERHEDE

6.1 Lys van onaktiewe bestanddele

Di-stearoïelfosfatidiel gliserol, Gehidrogeneerde soja fosfatidielcholien, Cholesterol NF, DL-Alfa-Tokoferol USP, Sukrose NF, Natriumsuksinaat dibasiese heksahidraat.

6.2 Onverenigbaarhede

Terisom is onverenigbaar met soutoplossings en mag nie gemeng word met ander medisinale produkte of elektroliete nie (sien afdeling 4.2).
Hierdie medisinale produk moet nie met ander medisinale produkte gemeng word nie, behalwe dié wat in afdeling 6.6 genoem word.

6.3 Rakleeftyd

36 Maande

Aangesien **TERISOM** nie enige bakteriostatiese middel bevat nie, moet die hersaamgestelde of verdunde produk, vanuit ‘n mikrobiologiese oogpunt, onmiddellik gebruik word.
In-gebruiks-bewaringstye en toestande voor toediening is die verantwoordelikheid van die gebruiker en is normaalweg nie langer as 24 uur teen 2-8 °C nie, tensy hersamestelling plaasgevind het onder gekontrolleerde en gevalideerde aseptiese toestande.
Die volgende chemiese en fisiese in-gebruiks-stabiliteitsdata is egter vir **TERISOM**

aangetoon:

Rakleeftyd na hersamestelling:
Glasflessies vir 24 uur by 25 ± 2 °C blootgestel aan daglig.
Glasflessies en polipropileenspuite tot 7 dae teen 2 – 8 °C
Moenie bevries nie.
MOENIE gedeeltelik-gebruikte flessies vir toekomstige pasiëntgebruik bewaar nie.

Rakleeftyd na verdunning met Dekstrose:
Tabel 4

Verdunnings-middel	Verdunning	Konsentrasie van amfoterisien-B mg/mL	Maksimum duur van bewaring by 2-8 ° C	Maksimum duur van bewaring by 25±2 ° C
5 % Dektrose	1 in 2	2.0	7 dae	48 uur
	1 in 8	0.5	7 dae	48 uur
	1 in 20	0.2	4 dae	24 uur
10 % Dektrose	1 in 2	2.0	48 uur	72 uur
20 % Dektrose	1 in 2	2.0	48 uur	72 uur

6.4 Spesiale voorsorgmaatreëls vir bewaring
TERISOM ongeopende flessies:
Moenie bo 25° C bewaar nie. Hou die flessies in die buitenste karton.
Vir bewaringstoestande na hersamestelling en verdunning van die medisinale produk, sien afdeling 6.3

6.5 Aard en inhoud van die houer
TERISOM word aangebied in 15 mL, 20 mL of 30 mL steriele, Tipe-I glasflessies. Die prop bestaan uit ‘n grys butielrubberprop en aluminiumringseël toegerus met ‘n plastiekdoppie wat verwyder kan word. Tien enkeldosis flessies word per karton verpak saam met 10 filters. Nie alle pakgroottes word noodwendig bemark nie.

6.6 Spesiale voorsorgmaatreëls vir vernietiging en ander hantering
LEES HIERDIE HELE AFDELING EN AFDELING 4.4 NOUKEURIG DEUR VOORDAT MET HERSAMESTELLING BEGIN WORD
TERISOM is nie gelykstaande aan ander amfoterisien produkte nie (sien afdeling 4.2).
TERISOM moet slegs saamgestel word deur Steriele Water vir Inspuiting (sonder ‘n bakteriostatiese middel) te gebruik en in Dektrose oplossing (5 %, 10 % of 20 %) verdun word slegs vir infusie.
Die gebruik van enige ander oplossing as dit wat aanbeveel word, of die teenwoordigheid van ‘n bakteriostatiese middel (bv. bensielalkohol) in die oplossing, kan presipitasie van **TERISOM** veroorsaak.

TERISOM is NIE verenigbaar met soutoplossing nie en moet nie hersaamgestel of verdun word met soutoplossing nie of deur ‘n intraveneuse lyn wat voorheen vir soutoplossing gebruik is, toegedien word nie, tensy dit eers met dektrose-oplossing (5 %, 10 % of 20 %) vir infusie gespoel is nie. Indien dit nie moontlik is nie, moet **TERISOM** deur ‘n aparte lyn toegedien word.
MOENIE **TERISOM** met ander medisinale produkte of elektroliete meng nie.
Aseptiese tegnieke moet streng toegepas word in alle hantering, aangesien geen preserveermiddel of bakteriostatiese middel in **TERISOM** teenwoordig is nie, of in die gespesifiseerde materiale vir hersamestelling en verdunning.
TERISOM moet deur behoorlik opgeleide personeel hersaamgestel word.
Flessies van **TERISOM** wat 50 mg amfoterisien bevat, word soos volg berei:

1. Voeg 12 ml Steriele Water vir Inspuiting by elke **TERISOM** flessie om ‘n preparaat wat 4 mg/mL amfoterisien bevat, te lewer.
2. ONMIDDELLIK na toevoeging van die water, moet DIE FLESSIE KRAGTIG geskud word vir 30 sekondes om die **TERISOM** volledig te versprei. Na hersamestelling is die konsentraat ‘n deurskynende, geel verspreiding. Ondersoek die flessie visueel vir deeltjies en hou aan skud totdat ‘n volledige verspreiding verkry is. Moenie gebruik as daar enige bewys van presipitasie van vreemde materiaal is nie.
3. Bereken die hoeveelheid van hersaamgestelde (4 mg/ml) **TERISOM** wat benodig word om verder te verdun (sien tabel hieronder).
4. Die infusie-oplossing word verkry deur die verdunning van die hersaamgestelde **TERISOM** met tussen een (1) en negentien (19) dele dekstrose-oplossing (5 %, 10 % of 20 %) vir infusie per volume, om ‘n finale konsentrasie in die aanbevole reeks van 2.00 mg/mL tot 0.20 mg/mL amfoterisien, as **TERISOM,** te verskaf (sien tabel hieronder).
5. Onttrek die berekende volume van die hersaamgestelde **TERISOM** in ‘n steriele spuit. Gebruik die 5-mikron filter wat voorsien word, drup die **TERISOM** preparaat in ‘n steriele houer met die korrekte hoeveelheid dektrose-oplossing (5 %, 10 % of 20 %) vir infusie.

‘n In-lyn membraanfilter kan vir intraveneuse infusie van **TERISOM** gebruik word. Die gemiddelde porie-deursnit van die filter moet egter nie minder as 1.0 mikron wees nie.

Voorbeeld van die bereiding van TERISOM verspreiding vir infusie teen ‘n dosis van 3mg/kg/dag in 5 % dektrose-oplossing vir infusie.

Tabel 5

Massa (kg)	Aantal flessies	Hoeveelheid **TERISOM** (mg)wat onttrek moet word vir verdere verdunning	Volume van hersaamgestelde **TERISOM** (mL)*	Om 'n 0.2 mg/mL konsentrasie te berei (1 in 20 verdunning)		Om 'n 2.0 mg/mL konsentrasie te berei (1 in 2 verdunning)	
				Volume van 5 % dekstrose wat benodig word (mL)	Totale volume (mL; **TERISOM** plus 5 % dektrose)	Volume van 5 % dektrose wat benodig word (mL)	Totale volume (mL; **TERISOM** plus 5 % dektrose)
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

* Elke flessie **TERISOM** (50 mg) word hersaamgestel met 12 mL Water vir Inspuiting om 'n konsentrasie van 4mg/mL amfoterisien-B te voorsien.

Enige ongebruikte produk of afvalmateriaal moet vernietig word in ooreenstemming met plaaslike vereistes.

7 HOUER VAN GOEDKEURING VIR BEMARKING

Ranbaxy Pharmaceuticals (Pty) Ltd
Lautreweg 14, Stormill, Uitbreiding 1
Roodepoort, 1724

8. GOEDKEURINGSNOMMER VIR BEMARKING

56/20.2.2/1125

9. DATUM VAN EERSTE GOEDKEURING

20 Junie 2023

10. DATUM VAN HERSIENING VAN DIE TEKS