IMPORTANT
MEDICINE SAFETY INFORMATION

Beware of different formulations and risk of medication errors: Fungizone® Intravenous (A/20.1.7/0150) and Ambisome® (36/20.2.2/0453)

Risks of medication errors with the different formulations of parenteral amphotericin B

24 May 2018

Dear Healthcare Professional,

In collaboration with the South African Health Products Regulatory Authority (SAHPRA) Bristol-Myers Squibb and Key Oncologics (Pty) Ltd would like to draw your attention to the risk of errors in prescribing, dispensing, preparing and administering different parenteral formulations of amphotericin B.

Amphotericin B for infusion is available in South Africa as a liposomal formulation (AmBisome®) and a non-lipid-based formulation (Fungizone® Intravenous). Errors are mainly related to the administration of Fungizone® Intravenous instead of AmBisome®, leading to amphotericin B overdose which could lead to serious cardiac or renal injury.

- **Parenteral amphotericin B formulations are not INTERCHANGABLE:** there is no possibility of substituting one amphotericin B medicinal product by another one.

- **Importance of recording the tradenames of products on the prescription** in order to avoid any risk of confusion between AmBisome® and Fungizone® Intravenous:
  - Verify the tradename and the prescribed dose before preparation and administration.
  - Specify the tradename when the prescription is made by INN (International Non-proprietary Name). There are no generic versions of either lipid or non-lipid-based amphotericin B formulations approved

- **Specific modalities of preparation and administration: (PLEASE SEE THE TABLE BELOW).**

The dosage and directions for use differ between the available formulations and are provided in the table hereafter.

<table>
<tr><th>Proprietary Name</th><th>Fungizone® Intravenous Injection</th><th>AmBisome® Intravenous Infusion</th></tr>
<tr><td>Dosage and Directions for Use</td><td>Fungizone® Intravenous should be administered by slow intravenous infusion. Intravenous infusion should be given over a period of approximately 2 to 6 hours observing the usual precautions for intravenous therapy. The recommended concentration for intravenous infusion is 0,1 mg/ml (1 mg/10 ml). Therapy is usually instituted with a daily dose of 0,25 mg/kg of body mass and gradually increased as tolerance permits.

Under no circumstances should a total daily dose of 1,5 mg/kg be exceeded.</td><td>AmBisome® should be administered by intravenous infusion over a 30 - 60 minute period. For doses greater than 5 mg/kg/day intravnous infusion over a 2 hour period is recommended. The recommended concentration for intravnous infusion is 0,20 mg/ml to 2,00 mg/ml amphotericin B.

<table><tr><th>Indication</th><th>Dose in mg/kg/day</th></tr><tr><td>Empirical therapy</td><td>3 mg</td></tr><tr><td>Systemic fungal infections</td><td>3 mg - 5 mg</td></tr><tr><td>Cryptococcal meningitis in HIV infected patients</td><td>6 mg</td></tr><tr><td>Visceral Leishmaniasis</td><td>Refer package insert</td></tr></table></td></tr>
<tr><td>Instructions for reconstitution and dilution</td><td>An initial concentrate of 5 mg amphotericin B per ml is first prepared by rapidly injecting 10 ml Sterile Water for Injection without a bacteriostatic agent directly into the lyophilised cake. The infusion solution is prepared taking sufficient* concentrate and diluting this with 5 % Dextrose Injection such that the final concentrate is 0,1 mg amphotericin B per ml. Do not reconstitute with saline solutions.</td><td>AmBisome® must be reconstituted using Sterile Water for Injection (without a bacteriostatic agent). Add 12 ml of Water for Injection to each AmBisome® vial, to yield a preparation containing 4 mg/ml amphotericin B. The infusion, providing from 2,00 mg to 0,20 mg amphotericin B per ml is obtained by dilution with one (1) to nineteen (19) parts respectively of a 5 %, 10 % or 20 % dextrose solution. AmBisome® is not physically compatible with saline and should not be mixed with other drugs or electrolytes.</td></tr>
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* Since patient tolerance varies greatly, the dosage of amphotericin B must be individualised and adjusted according to specific patient requirements (e.g. site and intensity of infection, etiologic agent). The infusion solution volume for each treatment will most likely vary depending on each patient's specific requirement, thus the volume taken from the initial dilution (amphotericin B 5 mg/ml) to prepare the infusion solution would need to be adjusted accordingly.

Carefully read and follow the instructions located on the package insert before performing any reconstitution/dilution of any parenteral amphotericin B formulation.

Healthcare professionals should report medication errors associated with parenteral amphotericin B to:

Healthcare professionals should report all adverse events associated with the use of Fungizone® Intravenous to Bristol-Myers Squibb (Pty) Ltd (South Africa) on 0800 444423 or e-mail, Medinfo.SouthAfrica@bms.com, alternatively to the SAHPRA Pretoria Office at Tel: 012 395 9133, Fax: 086 620 7253, Email: adr@health.gov.za OR National Adverse Drug Event Monitoring Centre at Tel: (021) 447 1618 or Fax: (021) 448 6181.	Healthcare professionals should report all adverse events associated with the use of Ambisome® Intravenous to Key Oncologics (Pty) Ltd on +27 79 471 1771 or e-mail safety@keyoncologics.co.za ; alternatively to the SAHPRA Pretoria Office at Tel: 012 395 9133, Fax: 086 620 7253, Email: adr@health.gov.za OR National Adverse Drug Event Monitoring Centre at Tel: (021) 447 1618 or Fax: (021) 448 6181.

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Should you have any questions or require additional information regarding the use of Fungizone® Intravenous, please contact 0800 444423 or e-mail Medinfo.SouthAfrica@bms.com.

Should you have any questions or require additional information regarding the use of Ambisome® Intravenous, please contact 011 483 0060 or e-mail key@icon.co.za

Yours sincerely

Bristol-Myers Squibb(Pty) Limited

K·E·Y ONCOLOGICS
Your Key Partner

Bristol-Myers Squibb (Pty) Ltd

Dr. Hennie Duvenhage
Pharmacovigilance Officer
Tel: (011) 808 5489
Fax: (011) 808 5302
E-mail: hennie.duvenhage@bms.com

Annelize de la Guerre
Responsible Pharmacist
Tel: (011) 808 5495
Fax (011) 808 5304
Email: annelize.delaguerre@bms.com

Key Oncologics (Pty) Ltd

Mari Nicolaides
Pharmacovigilance Officer
Tel: (011) 483 0060 /5
Fax: (011) 728 5060
E-mail: mari@keyoncologics.co.za

Jean Lambrechts
Responsible Pharmacist
Tel (011) 483 0060/5
Fax (011) 728 5060
Email: jean@keyoncologics.co.za