PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE
MICONONIN 50 mg powder for concentrate for solution for infusion.
MICONONIN 100 mg powder for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
MICONONIN 50 mg:
Each vial contains micafungin sodium equivalent to micafungin 50 mg.
After reconstitution, each ml contains micafungin sodium equivalent to micafungin 10 mg.
Contains sugar: lactose monohydrate 47,62 mg/ml.
MICONONIN 100 mg:
Each vial contains micafungin sodium equivalent to micafungin 100 mg.
After reconstitution, each ml contains micafungin sodium equivalent to micafungin 20 mg.
Contains sugar: lactose monohydrate 47,62 mg/ml.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
Lyophilized white to off-white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
MICONONIN is indicated for:
Adults, adolescents ≥ 16 years of age and elderly:
- Treatment of invasive candidiasis.
- Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.
- Prophylaxis of *Candida* infection in patients undergoing allogenic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for 10 or more days.

Children (including neonates) and adolescents < 16 years of age:
- Treatment of invasive candidiasis.
- Prophylaxis of *Candida* infection in patients undergoing allogenic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for 10 or more days.

Commonly susceptible species [MIC ranges in Europe, mg/l] in vitro
Candida albicans [0,007 – 0,25], *Candida glabrata* [0,007 – 0,12], *Candida tropicalis* [0,007 – 0,12], *Candida krusei* [0,015 – 0,12], *Candida kefyr* [0,03 – 0,06], *Candida parapsilosis* [0,12 – 2], *Candida guilliermondii* [0,5], *Candida lusitaniae* [0,12 – 0,25], *Candida* spp. [0,015 – 0,5] (incl. *C. famata, C. dubliniensis, C. lipolytica, C. pelliculosa, C. rugosa, C. stellatoidea* and *C. zeylanoides*), *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus terreus, Aspergillus nidulans, Aspergillus versicolor.* [(1)]
The mycelial form of dimorphic fungi (e.g. *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis*).

The decision to use MICONONIN should take into account a potential risk for the development of liver tumours MICONONIN should therefore only be used if other antifungals are not appropriate (see section 4.4).

4.2 Posology and method of administration
Posology
Treatment with MICONONIN should be initiated by a medical practitioner experienced in the management of fungal infections. Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly. The dose regimen of MICONONIN depends on the body weight of the patient as given in the following tables:

Use in adults, adolescents ≥ 16 years of age and elderly

Indication	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day
Treatment of oesophageal candidiasis	150 mg/day	3 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

* If the patient's response is inadequate, e.g., persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients ≤ 40 kg.

Use in children ≥ 4 months of age up to adolescents < 16 years of age

Indication	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

* If the patient's response is inadequate, e.g., persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients ≤ 40 kg.

Use in children (including neonates) < 4 months

Indication	
Treatment of invasive candidiasis	4 - 10 mg/kg/day*
Prophylaxis of Candida infection	2 mg/kg/day

* Micafungin dosed at 4 mg/kg in children less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. If central nervous system (CNS) infection is suspected, a higher dosage (e.g. 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS. The safety and efficacy in children (including neonates) less than 4 months of age of doses of 4 and 10 mg/kg for the treatment of invasive candidiasis with CNS involvement has not been adequately established in controlled clinical studies.

Treatment duration
Invasive candidiasis
The treatment duration of *Candida* infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and ***after*** resolution of clinical signs and symptoms of infection.

Oesophageal candidiasis
For the treatment of oesophageal candidiasis, MICONONIN should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of Candida infections
For prophylaxis of *Candida* infection, MICONONIN should be administered for at least one week after neutrophil recovery.

Special populations
Hepatic impairment
No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There are currently no data available for the use of MICONONIN in patients with severe hepatic impairment and its use is not recommended in these patients (see section 4.4 and 4.8).
Renal impairment
No dose adjustment is necessary in patients with renal impairment.

Paediatric population
Experience with MICONONIN in patients less than 2 years of age is limited.

Method of administration
For intravenous use.
After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour. More rapid infusions may result in more frequent histamine mediated reactions.
The reconstituted solution should be a clear transparent solution and free of visible particles as undissolved matter.
For reconstitution instructions see section 6.6.

4.3 Contraindications
- Hypersensitivity to micafungin or to any of the other excipients of MICONONIN (see section 6.1).

4.4 Special warnings and precautions for use
Hepatic effects
The development of foci of altered hepatocytes (FAH) and hepatocellular tumours after a treatment period of 3 months or longer were observed in rats. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The clinical relevance of this finding is not known. Liver function should be carefully monitored during micafungin treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended. Micafungin treatment should be conducted on a careful risk/benefit basis, particularly in patients having severe liver function impairment or chronic liver diseases known to represent preneoplastic conditions, such as advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects, or receiving a concomitant therapy including hepatotoxic and/or genotoxic properties.

Principles of antibiotics stewardship should be adhered to.

Data indicates that micafungin (as contained in MICONONIN) treatment was associated with significant impairment of liver function (increase of ALT, AST or total bilirubin > 3 times ULN) in both healthy volunteers and patients. In some patients more severe hepatic dysfunction, hepatitis, or hepatic failure including fatal cases have been reported. Paediatric patients < 1 year of age might be more prone to liver injury (see section 4.8).

Anaphylactic reactions
During administration of MICONONIN, anaphylactoid reactions including shock may occur. If these reactions occur, MICONONIN infusion should be discontinued, and appropriate treatment administered.

Skin reactions
Exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. If patients develop a rash, they should be monitored closely and MICONONIN discontinued if lesions progress.

Haemolysis
Cases of haemolysis, including acute intravascular haemolysis or haemolytic anaemia, have been reported in patients treated with micafungin (as in MICONONIN). Patients who develop clinical or laboratory evidence of haemolysis during MICONONIN therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing MICONONIN therapy.

Renal effects
MICONONIN may cause kidney problems, renal failure, and abnormal renal function test. Patients should be closely monitored for worsening of renal function.

Interactions with other medicines
A total of 14 clinical interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between micafungin and mycophenolate mofetil, ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, amphotericin B, itraconazole and voriconazole. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed. Exposure (AUC) of sirolimus was increased in the presence of micafungin (21 %). Patients receiving sirolimus in combination with micafungin should be monitored for sirolimus toxicity and the sirolimus dosage should be adjusted if necessary.

Pregnancy and breastfeeding
MICONONIN should not be used during pregnancy and breastfeeding (see section 4.6).

Paediatric population
The incidence of some adverse reactions was higher in paediatric patients than in adult patients (see section 4.8).

Lactose warning
MICONONIN contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not receive MICONONIN.

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

4.5 Interaction with other medicines and other forms of interaction
Micafungin has a low potential for interactions with medicines metabolised via CYP3A mediated pathways.

Interaction studies in healthy human subjects were conducted to evaluate the potential for interaction between micafungin and mycophenolate mofetil, ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, itraconazole, voriconazole and amphotericin B. In these studies, no evidence of altered pharmacokinetics of micafungin was observed. No MICONONIN dose adjustments are necessary when these medicines are administered concomitantly.
Exposure (AUC) of itraconazole, sirolimus and nifedipine was slightly increased in the presence of micafungin (22 %, 21 % and 18 % respectively).
Co-administration of micafungin and amphotericin B desoxycholate was associated with a 30 % increase in amphotericin B desoxycholate exposure. Since this may be of clinical significance this co-administration should only be used when the benefits clearly outweigh the risks, with close monitoring of amphotericin B desoxycholate toxicities (see section 4.4).
Patients receiving sirolimus, nifedipine or itraconazole in combination with MICONONIN should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (see section 4.4).

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no data from the use of MICONONIN in pregnant women. In animal studies micafungin crossed the placental barrier and reproductive toxicity was seen. The potential risk for humans is unknown.
MICONONIN should not be used during pregnancy.
Breastfeeding
It is not known whether MICONONIN is excreted in human breast milk. Animal studies have shown excretion of MICONONIN in breast milk.
MICONONIN should not be used during breastfeeding.
Fertility
Testicular toxicity was observed in animal studies. MICONONIN may have the potential to affect male fertility in humans.

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 performed. However, patients should be informed that somnolence and dizziness has been reported during treatment with MICONONIN (see section 4.8).

4.8 Undesirable effects
a. Summary of the safety profile
Overall, 32,2 % of the patients experienced adverse drug reactions. The most frequently reported adverse reactions were nausea, increased blood alkaline phosphatase, phlebitis (primarily in HIV infected patients with peripheral lines), vomiting, and increased aspartate aminotransferase. No clinically significant differences were seen when the safety data were analysed by gender or race.

b. Tabulated summary of adverse reactions
The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Leukopenia, neutropenia, anaemia
	Less frequent	Pancytopenia, thrombocytopenia, eosinophilia, hypoalbuminaemia, haemolytic anaemia, haemolysis (see section 4.4)
	Frequency unknown	Disseminated intravascular coagulation
Immune system disorders	Less frequent	Anaphylactic/anaphylactoid reaction, hypersensitivity
	Frequency unknown	Anaphylactic and anaphylactoid shock (see section 4.4)
Endocrine disorders	Less frequent	Hyperhidrosis
Metabolism and nutrition disorders	Frequent	Hypokalaemia, hypomagnesaemia, hypocalcaemia
	Less frequent	Hyponatraemia, hyperkalaemia, hypophosphataemia, anorexia
Psychiatric disorders	Less frequent	Insomnia, anxiety, confusion
Nervous system disorders	Frequent	Headache
	Less frequent	Somnolence, tremor, dizziness, dysgeusia
Cardiac disorders	Less frequent	Tachycardia, palpitations, bradycardia
Vascular disorders	Frequent	Phlebitis
	Less frequent	Hypotension, hypertension, flushing
	Frequency unknown	Shock
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, abdominal pain
	Less frequent	Dyspepsia, constipation
Hepato-biliary disorders	Frequent	Increased blood alkaline phosphatase, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin (including hyperbilirubinaemia), abnormal liver function test
	Less frequent	Hepatic failure (see section 4.4), increased gammaglutamyl-transferase, jaundice, cholestasis, hepatomegaly, hepatitis
	Frequency unknown	Hepatocellular damage including fatal cases (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Urticaria, pruritis, erythema [(2, 3)]
	Frequency unknown	Toxic skin eruption, erythema multiforme, Stevens-Johnson syndrome, toxic dermal necrolysis (see section 4.4)
Renal and urinary disorders	Less frequent	Increased blood creatinine, increased blood urea, aggravated renal failure
	Frequency unknown	Renal impairment (see section 4.4), acute renal failure
General disorders and administration site conditions	Frequent	Pyrexia, rigors
	Less frequent	Injection site thrombosis, infusion site inflammation, injection site pain, peripheral oedema
Investigations	Less frequent	Increased blood lactate dehydrogenase

c. Description of selected adverse reactions
Hepatic adverse reactions
Most hepatic adverse reactions were mild and moderate. Most frequent reactions were increase in AP, AST, ALT, blood bilirubin and abnormal liver function test. Few patients discontinued treatment due to a hepatic event. Cases of serious hepatic dysfunction occurred uncommonly (see section 4.4).

d. Paediatric population
Some adverse reactions (listed below) were higher in paediatric patients than in adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients. The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients. The proportion of paediatric patients with neutropenia was several-fold higher than in adult patients, as well as allogenic HSCT and haematological malignancy.

Blood and lymphatic system disorder
Frequent – thrombocytopenia
Cardiac disorder
Frequent – tachycardia
Vascular disorders
Frequent – hypertension, hypotension
Hepatobiliary disorders
Frequent – hyperbilirubinaemia, hepatomegaly
Renal and urinary disorders
Frequent – acute renal failure, increased blood urea

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions & Quality Problem Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose
There is no experience with overdoses of MICONONIN. In case of overdose, general supportive measures and symptomatic treatment should be administered. MICONONIN is highly protein-bound and not dialysable.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A.20.2.2 Antimicrobial (chemotherapeutic agents): Fungicides.
Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: J02AX05.

Mode of action
Micafungin non-competitively inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall. 1,3-β-D-glucan is not present in mammalian cells.
Micafungin exhibits fungicidal activity against most *Candida* species and prominently inhibits actively growing hyphae of *Aspergillus* species.

PK/PD relationship
Available data shows that an additive or synergistic pharmacodynamic interaction of micafungin and amphotericin B was found in a mouse model of pulmonary aspergillosis (immunosuppression with hydrocortisone, intranasal infection with Aspergillus fumigatus).

Mechanism(s) of resistance
Cases of reduced susceptibility and resistance have been reported and cross-resistance with other echinocandins cannot be excluded. Reduced susceptibility to echinocandins has been associated with mutations in the Fks1 gene coding for a major subunit of glucan synthase.

Inherently resistant organisms
Cryptococcus spp., Pseudallescheria spp., Scedosporium spp., Fusarium spp., Trichosporon spp., Zygomycetes spp.

5.2 Pharmacokinetic properties
Absorption
Pharmacokinetics is linear over the daily dose range of 12,5 mg to 200 mg and 3 mg/kg to 8 mg/kg.
There is no evidence of systemic accumulation with repeated administration and steady state is generally reached within 4 to 5 days.

Distribution
Following intravenous administration concentrations of micafungin show a bi-exponential decline. Micafungin is rapidly distributed into tissues. In systemic circulation, micafungin is highly bound to plasma protein (> 99 %), primarily to albumin.
Binding to albumin is independent of micafungin concentration (10-100 µg/ml).
The volume of distribution at steady state (Vss) was approximately 18-19 litres.

Biotransformation
Unchanged micafungin is the principal circulating compound in systemic circulation. Micafungin has been shown to be metabolised to several compounds; of these M-1 (catechol form), M-2 (methoxy form of M-1) and M-5 (hydroxylation at the side chain) of micafungin have been detected in systemic circulation. Exposure to these metabolites is low and metabolites do not contribute to the overall efficacy of micafungin. Even though micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*.

Elimination
The mean terminal half-life is approximately 10-17 hours and stays consistent across doses up to 8 mg/kg and after single and repeated administration. Total clearance was 0,15-0,3 ml/min/kg in healthy subjects and adult patients and is independent of dose after single and repeated administration. Following a single intravenous dose of ^{14}C-micafungin (25 mg) to healthy volunteers, 11,6 % of the radioactivity was recovered in the urine and 71,0 % in the faeces over 28 days. These data indicate that elimination of micafungin is primarily non-renal. In plasma, metabolites M-1 and M-2 were detected only at trace concentrations and metabolite M-5, the more abundant metabolite, accounted for a total of 6,5 % relative to parent compound.

Special population
Paediatric patients
In paediatric patients, micafungin exposure is dose proportional in the dose range of 0.5-4 mg/kg, and up to 10 mg/kg in infants less than 4 months of age. Clearance is influenced by weight with mean values of weight-adjusted clearance 1.35 times higher in the younger children (4 months to 5 years) and 1.14 times higher in children aged 6 to 11 years. Older children (12-16 years) had mean clearance values similar to those determined in adult patients. Mean weight-adjusted clearance in infants less than 4 months of age is approximately 2.6-fold greater than older children (12-16 years) and 2.3-fold greater than in adults. Weight-adjusted clearance differences support weight-based dosing up to body weights within the range of 40 (treatment) to 50 kg (prophylaxis), above which adult dosing is recommended.
Micafungin dosed at 4 mg/kg in infants less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. Higher doses (e.g., 10 mg/kg) may be required to treat CNS infection in infants less than 4 months of age as demonstrated by a PK-PD bridging study that showed dose-dependent penetration of micafungin into the CNS to achieve maximum eradication of fungal burden in the CNS tissues. Population PK modelling demonstrated that a dose of 10 mg/kg in infants less than 4 months of age would be sufficient to achieve the target exposure for the treatment of CNS
Candida infections.

Elderly
Available data indicates that when administered as a single 1-hour infusion of 50 mg the pharmacokinetics of micafungin in the elderly (aged 66-78 years) were similar to those in young (20-24 years) subjects. No dose adjustment is necessary for the elderly.

Patients with hepatic impairment
Available data from a study performed in patients with moderate hepatic impairment (Child -Pugh score 7-9), (n=8) shows that, the pharmacokinetics of micafungin did not significantly differ from those in healthy subjects (n=8). Therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. The pharmacokinetics of micafungin has not been studied in patients with severe hepatic insufficiency.

Patients with renal impairment
Severe renal impairment (Glomerular Filtration Rate [GFR] <30 ml/min) did not significantly affect the pharmacokinetics of micafungin. No dose adjustment is necessary for patients with renal impairment.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Citric acid anhydrous (E330) (to adjust the pH)
Lactose monohydrate
Sodium hydroxide (E524) (to adjust the pH)
Water for injection

6.2 Incompatibilities
This medicine must not be mixed or co-infused with other medicine except those mentioned in section 6.6.

6.3 Shelf life
Unopened vial
30 months
Reconstituted concentrate in vial
24 hours when reconstituted with sodium chloride 9 mg/ml (0,9 %) or dextrose 50 mg/ml (5 %) solution for infusion (Reconstituted concentrate in vial).
Diluted infusion solution
24 hours when diluted with sodium chloride 9 mg/ml (0,9 %) or dextrose 50 mg/ml (5 %) solution for infusion (Diluted solution for infusion).

6.4 Special precautions for storage
Store at or below 25 ºC in the original package in order to protect from light. This medicine can withstand direct light exposure for up to 60 days (2 months).
Reconstituted concentrate in vial
Store at or below 25 ºC, when reconstituted with sodium chloride 9 mg/ml (0,9 %) or dextrose 50 mg/ml (5 %) solution for infusion (Reconstituted concentrate in vial).
Diluted infusion solution
Store at or below 25 ºC protected from light, when diluted with sodium chloride 9 mg/ml (0,9 %) or dextrose 50 mg/ml (5 %) solution for infusion (Diluted solution for infusion).
From a microbial point of view, MICONONIN 50 mg and 100 mg powder for solution for infusion contains no preservatives; the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless the reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container
MICONONIN 50: 10 ml Type I glass vial closed with an isobutylene isoprene rubber stopper and an aluminium seal with a blue plastic, flip-of cap.
MICONONIN 100: 10 ml Type I glass vial closed with an isobutylene isoprene rubber stopper and an aluminium seal with a red plastic, flip-of cap.
The vial is wrapped with a UV-protective film.
Pack size: one vial per cardboard carton.

6.6 Special precautions for disposal and other handling
The reconstituted solution should be a clear transparent solution and free of visible particles as undissolved matter.
Any unused medicine or waste material should be disposed of in accordance with local requirements.
Instructions for reconstitution and dilution
MICONONIN must not be mixed or co-infused with other medicines except those mentioned below.
MICONONIN is reconstituted and diluted as follows:
- The plastic cap must be removed from the vial and the stopper disinfected with alcohol.
- 5 ml of the sodium chloride 9 mg/ml (0,9 %) solution for infusion or glucose 50 mg/ml (5 %) solution for infusion (taken from a 100 ml bottle/bag) should be aseptically and slowly injected into each vial along the side of the inner wall. Although the concentrate will foam, every effort should be made to minimise the amount of foam generated. A sufficient number of vials of MICONONIN must be reconstituted to obtain the required dose in mg (see table below).
- The vial should be rotated gently. DO NOT SHAKE. The powder will dissolve completely. The concentrate should be used immediately. The vial is for single use only. Therefore, please discard unused reconstituted concentrate immediately.
- All of the reconstituted concentrate should be withdrawn from each vial and returned into the infusion bottle/bag from which it was originally taken. The diluted infusion solution should be used immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C when protected from light and diluted as described above.
- The infusion bottle/bag should be gently inverted to disperse the diluted solution but NOT agitated in order to avoid foaming. Do not use if the solution is cloudy or has precipitated.
- The infusion bottle/bag containing the diluted infusion should be inserted into a closable opaque bag for protection from light.

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour.
Preparation of the solution for infusion:

Dose (mg)	MICONONIN vial to be used (mg/vial)	Volume of sodium chloride 9 mg/ml (0,9 %) or glucose 50 mg/ml (5 %) to be added per vial	Volume (concentration) of reconstituted powder	Standard infusion (added up to 100 ml) Final concentration
50	1 x 50	5 ml	Approx. 5 ml (10 mg/ml)	0,5 mg/ml
100	1 x 100	5 ml	Approx. 5 ml (20 mg/ml)	1,0 mg/ml
150	1 x 100 + 1 x 50	5 ml	Approx. 10 ml	1,5 mg/ml
200	2 x 100	5 ml	Approx. 10 ml	2,0 mg/ml

7 HOLDER OF CERTIFICATE OF REGISTRATION
Kahma Biotech (Pty) Ltd
106, 16th Road
Midrand
1686
South Africa

8 REGISTRATION NUMBERS
MICONONIN 50 mg: 56/20.2.2/0533
MICONONIN 100 mg: 56/20.2.2/0534

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26 March 2024

10 DATE OF REVISION OF THE TEXT
N.A