PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

MICAFUNGIN 50 mg ADCO (Powder for solution for infusion)

MICAFUNGIN 100 mg ADCO (Powder for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MICAFUNGIN 50 mg ADCO: Each vial contains 50 mg of micafungin (as sodium salt)

MICAFUNGIN 100 mg ADCO: Each vial contains 100 mg of micafungin (as sodium salt)

Contains sugar. Lactose monohydrate 50 mg/ml

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

White lyophilised cake or powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MICAFUNGIN ADCO 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 allogeneic 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 allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for 10 or more days.

The decision to use **MICAFUNGIN ADCO** should take into account a potential risk for the development of liver tumours. **MICAFUNGIN ADCO** 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 **MICAFUNGIN ADCO** 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 **MICAFUNGIN ADCO** depends on the body weight of the patient as given in the following table:

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.

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, **MICAFUNGIN ADCO** should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of *Candida* infections:

For prophylaxis of *Candida* infection, **MICAFUNGIN ADCO** 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 (see section 5.2). There are currently insufficient data available for the use of **MICAFUNGIN ADCO** in patients with severe hepatic impairment and its use is not recommended in these patients (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Paediatric population

Experience with **MICAFUNGIN ADCO** in patients less than 2 years of age is limited.

Method of administration

Precaution to be taken before manipulating or administering the product.

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.

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of **MICAFUNGIN ADCO** listed in 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 was observed in rats. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The relevance of this finding for the therapeutic use in patients cannot be excluded. Liver function should be carefully monitored during MICAFUNGIN ADCO 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 ADCO 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.

Micafungin 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 **MICAFUNGIN ADCO**, anaphylactoid reactions, including shock, may occur. If these reactions occur, **MICAFUNGIN ADCO** infusion should be discontinued, and appropriate treatment administered.

Symptoms such as rash and rigors may occur. They may be mild to moderate in intensity and not treatment limiting.

Serious reactions (e.g. anaphylactoid reactions) were commonly reported during therapy with micafungin and only in patients with serious underlying conditions (e.g. advanced AIDS, malignancies) requiring multiple co-medications.

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 **MICAFUNGIN ADCO** discontinued if lesions progress.

Haemolysis

Cases of haemolysis, including acute intravascular haemolysis or haemolytic anaemia, may occur in patients treated with **MICAFUNGIN ADCO**. Patients who develop clinical or laboratory evidence of haemolysis during **MICAFUNGIN ADCO** therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing **MICAFUNGIN ADCO** therapy.

Renal effects

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

Interactions with other medicinal products

Co-administration of micafungin and amphotericin B desoxycholate should only be used when the benefits clearly outweigh the risks, with close monitoring of amphotericin B desoxycholate toxicities (see section 4.5).

Patients receiving sirolimus, nifedipine or itraconazole in combination with micafungin should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (see section 4.5).

Paediatric population

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

4.5. Interactions with other medicines and other forms of interaction

MICAFUNGIN ADCO 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 **MICAFUNGIN ADCO** dose adjustments are necessary when these medicines are administered concomitantly.

Exposure (AUC) of itraconazole, sirolimus and nifedipine may be slightly increased in the presence of **MICAFUNGIN ADCO**.

Patients receiving sirolimus, nifedipine or itraconazole in combination with **MICAFUNGIN ADCO** 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).

Co-administration of **MICAFUNGIN ADCO** and amphotericin B desoxycholate may be 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).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females:

The use of **MICAFUNGIN ADCO** in women of childbearing potential should be given when appropriate contraceptive measures are taken.

Pregnancy

There are no data from the use of **MICAFUNGIN ADCO** in pregnant women. In animal studies micafungin crossed the placental barrier and reproductive toxicity was seen. The potential risk for humans is unknown.

MICAFUNGIN ADCO should not be used during pregnancy.

Breast-feeding

MICAFUNGIN ADCO should not be used during breastfeeding. It is not known whether micafungin is excreted in human breast milk. Animal studies have shown excretion of micafungin in breast milk.

Fertility

Testicular toxicity was observed in animal studies. **MICAFUNGIN ADCO** may have the potential to affect male fertility in humans.

4.7 Effects on ability to drive and use machines

MICAFUNGIN ADCO has no or negligible influence on the ability to drive and use machines. However, adverse reactions, such as dizziness have been reported during treatment which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reactions may be nausea, blood alkaline phosphatase increase, phlebitis (primarily in HIV infected patients with peripheral lines), vomiting and aspartate aminotransferase increased.

b. Tabulated summary of adverse reactions

Blood and lymphatic system disorders	
Frequent	Leukopenia, neutropenia, anaemia
Less frequent	Pancytopenia, thrombocytopenia, eosinophilia, hypoalbuminaemia, haemolytic anaemia, haemolysis
Frequency not known	Disseminated intravascular coagulation
Immune system disorders	
Less frequent	Anaphylactic/anaphylactoid reaction, hypersensitivity
Frequency not known	Anaphylactic and anaphylactoid shock
Endocrine disorders	
Less frequent	Hyperhidrosis

Metabolism and nutritional 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 not known	Shock
Respiratory, thoracic and mediastinal disorders	
Less frequent	Dyspnoea
Gastrointestinal disorders	
Frequent	Nausea, vomiting, diarrhoea, abdominal pain
Less frequent	Dyspepsia, constipation
Hepatobiliary 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, increased gammaglutamyltransferase, jaundice, cholestasis, hepatomegaly, hepatitis
Frequency not known	Hepatocellular damage including fatal cases

Skin and subcutaneous tissue disorders	
Frequent	Rash
Less frequent	Urticaria, pruritus, erythema
Frequency not known	Toxic skin eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary disorders	
Less frequent	Increased blood creatinine, increased blood urea, aggravated renal failure
Frequency not known	Renal impairment, 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

Possible allergic-like symptoms

Symptoms such as rash and rigors have been reported in clinical studies. The majority were of mild to moderate intensity and not treatment limiting. Serious reactions (e.g. anaphylactoid reaction 0,2 %, 6/3028) were less frequently reported during therapy with micafungin and only in patients with serious underlying conditions (e.g. advanced AIDS, malignancies) requiring multiple co-medications.

Hepatic adverse reactions

The overall incidence of hepatic adverse reactions in the patients treated with micafungin in clinical studies was 8,6 % (260/3028). The majority of hepatic adverse reactions were mild and moderate. Most frequent reactions were increase in AP (2,7 %), AST (2,3 %), ALT (2,0 %), blood bilirubin (1,6 %) and liver function test abnormal (1,5 %). Few patients (1,1 %; 0,4 % serious) discontinued treatment

due to a hepatic event. Cases of serious hepatic dysfunction occurred less frequently (see section 4.4).

Injection-site reactions

None of the injection-site adverse reactions were treatment limiting.

d. Paediatric population

The incidence of some adverse reactions (listed in the table below) was 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 (see section 4.4). The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients observed in clinical studies. At the time of entering the study, the proportion of paediatric patients with neutropenia was several-fold higher than in adult patients (40,2 % and 7,3 % of children and adults, respectively), as well as allogeneic HSCT (29,4 % and 13,4 %, respectively) and haematological malignancy (29,1 % and 8,7 %, respectively).

Blood and lymphatic system disorders

Frequent: thrombocytopenia

Cardiac disorders

Frequent: tachycardia

Vascular disorders

Frequent: hypertension, hypotension

Hepatobiliary disorders

Frequent: hyperbilirubinaemia, hepatomegaly

Renal and urinary disorders

Frequent: acute renal failure, blood urea increased

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 Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

Repeated daily doses up to 8 mg/kg (maximum total dose 896 mg) in adult patients have been administered in clinical trials with no reported dose-limiting toxicity. There is no experience with overdoses of **MICAFUNGIN ADCO**. In case of overdose, general supportive measures and symptomatic treatment should be administered. **MICAFUNGIN ADCO** is highly protein-bound and not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: J02AX05

Mechanism 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

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 and Fks2 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 are 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 biexponential 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 and excretion

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.

Pharmacokinetic/pharmacodynamic relationships

Pharmacokinetic/pharmacodynamic bridging study demonstrated dose-dependent penetration of micafungin into CNS with the minimum AUC of 170 µg*hr/L required to achieve maximum eradication of fungal burden in the CNS tissues. Population pharmacokinetic modelling demonstrated that a dose of 10 mg/kg in children less than 4 months of age would be sufficient to achieve the target exposure for the treatment of CNS *Candida* infections.

Special populations:

Paediatric population

In paediatric patients AUC values were dose proportional over the dose range of 0,5-4 mg/kg. Clearance was influenced by age, with mean values of clearance in younger children (2-11 years) being approximately 1,3-fold greater than those in older children (12-17 years). Older children had mean clearance values similar to those determined in adult patients. Mean clearance in premature infants (gestational age approximately 26 weeks) is approximately 5-fold greater than in adults.

Elderly

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.

Hepatic impairment

In a study performed in patients with moderate hepatic impairment (Child-Pugh score 7-9), the pharmacokinetics of micafungin did not significantly differ from those in healthy subjects. 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.

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.

Gender/Race

Gender and race (Caucasian, Black and Oriental) did not significantly influence the pharmacokinetic parameters of micafungin. No dose adjustment of micafungin is required based on gender or race.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Citric acid anhydrous

Sodium hydroxide

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 2 years

Reconstituted concentrate in vial

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 25 °C when reconstituted with sodium chloride 0,9 % and glucose 5 %.

Diluted infusion solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C when reconstituted with sodium chloride 0,9 % and glucose 5 %.

MICAFUNGIN ADCO contains no preservatives. From a microbiological point of view, 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 25 °C, unless the reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after reconstitution and dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

MICAFUNGIN 50 mg ADCO: 10 ml Type I clear glass vial with a bromobutyl double slotted rubber stopper and an aluminium flip off seal with royal blue colour button.

MICAFUNGIN 100 mg ADCO: 10 ml Type I clear glass vial with a bromobutyl double slotted rubber stopper and an aluminium flip off seal with red colour button.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

MICAFUNGIN ADCO must not be mixed or co-infused with other medicines except those mentioned below. Using aseptic techniques at room temperature, **MICAFUNGIN ADCO** is reconstituted and diluted as follows:

1. The plastic cap must be removed from the vial and the stopper disinfected with alcohol.
2. Five ml of 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 **MICAFUNGIN ADCO** must be reconstituted to obtain the required dose in mg (see table below).
3. 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, unused reconstituted concentrate must be discarded immediately.
4. 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.

5. The infusion bottle/bag should be gently inverted to disperse the diluted solution but NOT agitated in order to avoid foaming. The solution must not be used if it is cloudy or has precipitated.
6. The infusion bottle/bag containing the diluted infusion solution should be inserted into a closable opaque bag for protection from light.

Preparation of the solution for infusion

Dose (mg)	**MICAFUNGIN ADCO vial to be used (mg/vial)**	**Volume of sodium chloride (0,9 %) or glucose (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	Approximately 5 ml (10 mg/ml)	0,5 mg/ml
100	1 x 100	5 ml	Approximately 5 ml (20 mg/ml)	1,0 mg/ml
150	1 x 100 + 1 x 50	5 ml	Approximately 10 ml	1,5 mg/ml
200	2 x 100	5 ml	Approximately 10 ml	2,0 mg/ml

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd
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2013
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8. REGISTRATION NUMBER(S)

MICAFUNGIN 50 mg ADCO: 55/20.2.2/0666

MICAFUNGIN 100 mg ADCO: 55/20.2.2/0667

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 May 2023

10. DATE OF REVISION OF THE TEXT

23 May 2023

PI 23 May 2023