PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Arandi™ 100 mg (Powder for concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ARANDI 100 mg vial contains 100 mg anidulafungin.

The reconstituted solution contains 3,33 mg/ml anidulafungin and the diluted solution contains 0,77 mg/ml anidulafungin.

Excipients:

Contains sugar: 100 mg fructose per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white cake or powder.

The reconstituted solution has a pH of 3,5 to 5,5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ARANDI 100 mg is indicated for the treatment of invasive candidiasis, including candidaemia, in adult patients.

4.2. Posology and method of administration

Posology:

Invasive candidiasis, including candidaemia, in adult patients:

A single 200 mg loading dose should be administered on day 1, followed by 100 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

Special populations:

Use in renal and hepatic impairment:

No dosing adjustments are required for patients with mild, moderate, or severe hepatic impairment. Hepatic function should be monitored.

No dosing adjustments are required for patients with any degree of renal insufficiency, including those on dialysis. ARANDI 100 mg can be given without regard to the timing of haemodialysis (see section 5.2).

Use in other special populations:

No dosing adjustments are required for adult patients based on patient gender, weight, ethnicity, HIV positivity, or elderly status.

Use in children and adolescents:

ARANDI 100 mg should not be used in children.

Method of administration:

ARANDI 100 mg should be reconstituted with water for injections to a concentration of 3,33 mg/ml and subsequently diluted to a concentration of 0,77 mg/ml before use according to the instructions given in section 6.6.

It is recommended that ARANDI 100 mg is administered at a maximum rate of infusion that does not exceed 1,1 mg/minute. The rate of infusion is equivalent to 1,4 ml/min for the 100 mg and 200 mg doses.

For single use only.

4.3. Contraindications

- Hypersensitivity to anidulafungin or to any of the excipients in ARANDI 100 mg listed in section 6.1.
- Hypersensitivity to other medicines of the echinocandin class (e.g. caspofungin).
- Pregnancy and lactation.
- Use in patients under 18 years of age.

4.4. Special warnings and precautions for use

ARANDI 100 mg has not been studied in patients with *Candida endocarditis*, osteomyelitis or meningitis.

The efficacy of ARANDI 100 mg has only been evaluated in a limited number of neutropenic patients.

Hepatic effects:

Increased levels of hepatic enzymes have been seen in healthy subjects and patients treated with anidulafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medicines along with anidulafungin, clinically significant hepatic abnormalities have occurred. Cases of significant hepatic dysfunction, hepatitis, and hepatic failure were uncommon in clinical trials. Patients with increased hepatic enzymes during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.

Anaphylactic reactions:

Anaphylactic reactions, including shock, were reported with the use of anidulafungin. If these reactions occur, anidulafungin should be discontinued and appropriate treatment administered.

Infusion-related reactions:

Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnoea, bronchospasm and hypotension. Infusion-related adverse events are infrequent when the rate of anidulafungin infusion does not exceed 1,1 mg/min (see section 4.8).

Exacerbation of infusion-related reactions by co-administration of anaesthetics has been seen in a non-clinical (rat) study (see section 5.3). The clinical relevance of this is unknown. Nevertheless, care should be taken when co-administering anidulafungin and anaesthetic medicines.

Fructose content:

Patients with rare hereditary problems of fructose intolerance should not take ARANDI 100 mg.

A detailed history with regard to hereditary fructose intolerance symptoms has to be taken from each patient prior to being given this medicine.

4.5. Interaction with other medicines and other forms of interaction

Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A). Of note, *in vitro* studies do not fully exclude possible *in vivo* interactions.

Interaction studies were performed with anidulafungin and other medicines likely to be co-administered. No dosage adjustment of either medicine is recommended when anidulafungin is co-administered with ciclosporin, voriconazole or tacrolimus, and no dosage adjustment for anidulafungin is recommended when co-administered with amphotericin B or rifampicin.

Paediatric population:

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no data from the use of anidulafungin in pregnant women. Studies in animals have shown reproductive toxicity.

Breastfeeding:

It is unknown whether anidulafungin is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of anidulafungin in milk.

Fertility:

For anidulafungin, there were no effects on fertility in studies conducted in male and female rats.

4.7. Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Summary of the safety profile:

Infusion-related adverse reactions have been reported with anidulafungin in clinical studies, including rash, pruritus dyspnoea, bronchospasm, hypotension (frequent events), flushing, hot flush and urticaria (less frequent events), summarised in Table 1 (see section 4.4).

The following table includes the all-causality adverse reactions (MedDRA terms) from subjects who received 100 mg anidulafungin. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Table of Adverse Reactions

System Organ Class	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and Infestations		Fungaemia, candidiasis, pseudomembranous colitis, oral candidiasis	
Blood and Lymphatic System Disorders	Thrombocytopenia, coagulopathy	Thrombocythaemia	
Immune System Disorders			Anaphylactic shock, anaphylactic reaction*
Metabolism and	Hyperkalaemia, hypokalaemia,	Hypercalcaemia, hypernatraemia	

Nutrition Disorders	hyperglycaemia, hypomagnesaemia		
Nervous System Disorders	Convulsion, headache		
Eye Disorders		Eye pain, visual disturbance, vision blurred	
Cardiac Disorders		Atrial fibrillation, sinus dysrhythmia, ventricular extrasystoles, bundle branch block right	
Vascular Disorders	Flushing, hypotension, hypertension	Thrombosis, hot flush	
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm, dyspnoea		
Gastrointestinal Disorders	Diarrhoea, nausea, vomiting	Abdominal pain upper, faecal incontinence, constipation	
Hepatobiliary Disorders	Gamma-Glutamyltransferase increased, alanine aminotransferase increased, blood alkaline phosphatase	Liver function test abnormal, hepatic enzyme increased, transaminases increased	

	increased, aspartate aminotransferase increased, blood bilirubin increased, cholestasis		
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	Urticaria, generalised pruritus	
Renal and Urinary Disorders	Blood creatinine increased		
Musculoskeletal and Connective Tissue Disorders		Back pain	
General Disorders and Administration Site Conditions		Infusion site pain	
Investigations	Prolonged electrocardiogram QT	Increased blood amylase, decreased blood magnesium, decreased blood potassium, electrocardiogram abnormal, increased lipase,	

		increased platelet count, increased blood urea	

*See section 4.4

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 Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.
Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

In case of overdose, adverse reactions may occur as mentioned in section 4.8 and general supportive measures should be utilised as necessary.

During clinical trials, a single 400 mg dose of anidulafungin was inadvertently administered as a loading dose. No clinical adverse reactions were reported. No dose limiting toxicity was observed in a study of 10 healthy subjects administered a loading dose of 260 mg followed by 130 mg daily; 3 of the 10 subjects experienced transient, asymptomatic transaminase elevations (≤3 x Upper Limit of Normal (ULN)).

ARANDI 100 mg is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: JO2AX06
Pharmacological classification; A20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics.

Mechanism of action:

Anidulafungin is a semi-synthetic echinocandin, a lipopeptide synthesised from a fermentation product of *Aspergillus nidulans*.

Anidulafungin selectively inhibits 1,3-β-D glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. Anidulafungin has shown fungicidal activity against *Candida* species and activity against regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

5.2. Pharmacokinetic properties

General pharmacokinetic characteristics:

The pharmacokinetics of anidulafungin have been characterised in healthy subjects, special populations and patients. A low intersubject variability in systemic exposure (coefficient of variation ~25 %) was observed. The steady state was achieved on the first day after a loading dose (twice the daily maintenance dose).

Distribution:

The pharmacokinetics of anidulafungin are characterised by a rapid distribution half-life (0,5 to 1 hour) and a volume of distribution, 30 to 50 L, which is similar to total body fluid volume. Anidulafungin is extensively bound (>99 %) to human plasma proteins.

Biotransformation:

Hepatic metabolism of anidulafungin has not been observed. Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes. It is unlikely that anidulafungin will have clinically relevant effects on the metabolism of medicines metabolised by cytochrome P450 isoenzymes.

Anidulafungin undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide that lacks antifungal activity. The *in vitro* degradation half-life of anidulafungin under physiologic conditions is approximately 24 hours. *In vivo*, the ring-opened product is subsequently converted to peptidic degradants and eliminated mainly through biliary excretion.

Elimination:

The clearance of anidulafungin is about 1 L/h. Anidulafungin has a predominant elimination half-life of approximately 24 hours that characterises the majority of the plasma concentration-time profile, and a terminal half-life of 40 to 50 hours that characterises the terminal elimination phase of the profile.

In a single-dose clinical study, radiolabeled (14C) anidulafungin (~88 mg) was administered to healthy subjects. Approximately 30 % of the administered radioactive dose was eliminated in the faeces over 9 days, of which less than 10 % was intact medicine. Less than 1 % of the administered radioactive dose was excreted in the urine, indicating negligible renal clearance. Anidulafungin concentrations fell below the lower limits of quantitation 6 days post-dose. Negligible amounts of drug-derived radioactivity were recovered in blood, urine, and faeces 8 weeks post-dose.

Linearity:

Anidulafungin displays linear pharmacokinetics across a wide range of once daily doses (15 to 130 mg).

Special Populations:

Patients with fungal infections:

The pharmacokinetics of anidulafungin in patients with fungal infections are similar to those observed in healthy subjects based on population pharmacokinetic analyses. With the 200/100 mg daily dose regimen at an infusion rate of 1,1 mg/min, the steady state C_{max} and trough concentrations (C_{min}) could reach approximately 7 and 3 mg/L, respectively, with an average steady state AUC of approximately 110 mg.h/L.

Weight:

Although weight was identified as a source of variability in clearance in the population pharmacokinetic analysis, weight has little clinical relevance on the pharmacokinetics of anidulafungin.

Gender:

Plasma concentrations of anidulafungin in healthy men and women were similar. In multiple-dose patient studies, medicine clearance was slightly faster (approximately 22 %) in men.

Elderly:

The population pharmacokinetic analysis showed that median clearance differed slightly between the elderly group (patients ≥ 65, median CL = 1,07 L/h) and the non-elderly group (patients < 65, median CL = 1,22 L/h), however the range of clearance was similar.

Ethnicity:

Anidulafungin pharmacokinetics were similar among Caucasians, Blacks, Asians, and Hispanics.

HIV positivity:

Dosage adjustments are not required based on HIV positivity, irrespective of concomitant anti-retroviral therapy.

Hepatic insufficiency:

Anidulafungin is not hepatically metabolised. Anidulafungin pharmacokinetics were examined in subjects with Child-Pugh class A, B or C hepatic insufficiency. Anidulafungin concentrations were not increased in subjects with any degree of hepatic insufficiency. Although a slight decrease in AUC was observed in patients with Child-Pugh C hepatic insufficiency, the decrease was within the range of population estimates noted for healthy subjects.

Renal insufficiency:

Anidulafungin has negligible renal clearance (<1 %). In a clinical study of subjects with mild, moderate, severe or end stage (dialysis-dependent) renal insufficiency, anidulafungin pharmacokinetics were similar to those observed in subjects with normal renal function. Anidulafungin is not dialysable and may be administered without regard to the timing of haemodialysis.

Paediatric population:

Safety and efficacy in children have not been established.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Fructose, mannitol, polysorbate 80, *(S)*-lactic acid, sodium hydroxide (for pH-adjustment), hydrochloric acid, concentrated (for pH-adjustment)

6.2. Incompatibilities

ARANDI 100 mg must not be mixed or co-administered with other medicines or electrolytes except those mentioned in section 6.6.

Parenteral medicine products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If particulate matter or discolouration are identified, discard the solution.

6.3. Shelf life

36 months

Reconstituted solution:

The reconstituted solution may be stored at up to 25 °C for up to 24 hours.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25 °C.

From a microbiological point of view, following good aseptic practices, the reconstituted solution can be utilised for up to 24 hours when stored at 25 °C.

Infusion solution:

The infusion solution may be stored at 25 °C for 48 hours.

Do not freeze.

Chemical and physical in-use stability of the infusion solution has been demonstrated for 48 hours at 25 °C.

From a microbiological point of view, following good aseptic practices, the infusion solution can be utilised for up to 48 hours from preparation when stored at 25 °C.

6.4. Special precautions for storage

Store in a refrigerator (2 °C to 8 °C). Do not freeze.

Excursions for 96 hours up to 25 °C are permitted, and the powder can be returned to refrigerated storage.

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

6.5. Nature and contents of container

30 ml colourless type I glass vial with a bromobutyl rubber stopper coated with fluorinated polymer and aluminium flip-off cap with grey coloured polypropylene disks. ARANDI 100 mg powder for concentrate for solution for infusion is packed in a carton with an enclosed leaflet.

Pack size of 1 vial.

6.6. Special precautions for disposal and other handling

Reconstitution:

ARANDI 100 mg must be reconstituted with water for injections and subsequently diluted with ONLY 9 mg/ml (0,9 %) sodium chloride for infusion or 50 mg/ml (5 %) glucose for infusion. The compatibility of reconstituted ARANDI 100 mg with intravenous substances, additives, or medications other than 9 mg/ml (0,9 %) sodium chloride for infusion or 50 mg/ml (5 %) glucose for infusion has not been established. Aseptically reconstitute each vial with 30 ml water for injections to provide a concentration of 3,33 mg/ml. The reconstituted solution should be clear and free from visible particulates. The reconstituted solution must be further diluted within an hour.

Dilution and Infusion:

Aseptically transfer the contents of the reconstituted vial(s) into an IV bag (or bottle) containing either 9 mg/ml (0,9 %) sodium chloride for infusion or 50 mg/ml (5 %) glucose for infusion to obtain the appropriate ARANDI 100 mg concentration. The table below provides the volumes required for each dose.

Dilution requirements for ARANDI 100 mg administration

Dose	**Number of Vials Required**	**Total Reconstituted Volume**	**Infusion Volume [A]**	**Total Infusion Volume [B]**	**Rate of infusion**	**Minimum Duration**

		Required				
100 mg	1 (100 mg)	30 ml	100 ml	130 ml	1,4 ml/min	90 min
200 mg	2 (200 mg)	60 ml	200 ml	260 ml	1,4 ml/min	180 min

[A] Either 9 mg/ml (0,9 %) sodium chloride for infusion or 50 mg/ml (5 %) glucose for infusion.

[B] Infusion solution concentration is 0,77 mg/ml.

There are no special requirements for disposal.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

55/20.1.7/0530

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 August 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.

[1]Company Reg. No.: 1990/001979/07