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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ANIDULAFUNGIN ACCORD 100 mg (Powder for concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg anidulafungin. After reconstitution, each mL of suspension contains 3,33 mg/ml anidulafungin and the diluted solution contains 0,77 mg/ml anidulafungin.

Excipient with known effect:

Fructose 102,5 mg per vial

Mannitol 512,5 mg 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

ANIDULAFUNGIN ACCORD 100 mg is indicated for treatment of invasive candidiasis, including candidaemia, in adults and paediatric patients 1 month of age and older (see section 4.4).

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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 positive culture.

Special populations

Use in renal and hepatic impairment

No dosing adjustments are required for patients with renal (including those on dialysis) or hepatic impairment. Hepatic function should be monitored (see section 5.2).

Use in other special populations

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

Paediatric population

Use in children and adolescents 1 month to <18 years (dosing and treatment duration)

A single loading dose of 3,0 mg/kg (not to exceed 200 mg) should be administered on Day 1 followed by a daily maintenance dose of 1,5 mg/kg (not to exceed 100 mg) 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.

The safety and efficacy of anidulafungin have not been established in neonates (< 1 month old) (see section 4.4).

Method of administration

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For intravenous use.

For instructions on reconstitution and dilution of ANIDULAFUNGIN ACCORD, see section 6.6.

ANIDULAFUNGIN ACCORD should be reconstituted with water for injections to concentration of 3,33 mg/ml and subsequently diluted to a concentration of 0,77 mg/ml before use according to the instructions in section 6.6.
For a paediatric patient, the volume of infusion solution required to deliver the dose will vary depending on the weight of the child

It is recommended that ANIDULAFUNGIN ACCORD is administered at a maximum rate of infusion that does not exceed 1,1 mg/minute (see section 4.4). 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

- ANIDULAFUNGIN ACCORD is contra-indicated in patients with a known hypersensitivity to anidulafungin or to any of the exipients listed in section 6.1.
- Hypersensitivity to other medicines of the echinocandin class (e.g. caspofungin).

4.4 Special warnings and precautions for use

Anidulafungin has not been studied in patients with *Candida* endocarditis, osteomyelitis or meningitis. The efficacy of anidulafungin has only been evaluated in a limited number of neutropenic patients (see section 5.1).

Hepatic effects

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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 have been reported. Patients with increased hepatic enzymes during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for continuing anidulafungin therapy. However, if deteriorating hepatic function is persistent, ANIDULAFUNGIN ACCORD therapy should be withdrawn.

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. The clinical relevance of this is unknown. Nevertheless, care should be taken when co-administering anidulafungin and anaesthetic medicines.

Fructose content

ANIDULAFUNGIN ACCORD contains fructose.

Patients with hereditary fructose intolerance (HFI) should not be given this medicine unless strictly necessary.

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Babies and young children (below 2 years of age) may not yet be diagnosed with HFI. Medicines (containing fructose) given intravenously may be life-threatening and should not be administered in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicine.

Sodium content

ANIDULAFUNGIN ACCORD contains less than 1 mmol sodium (23 mg) per vial. Patients on low sodium diets can be informed that this medicine is essentially 'sodium-free'.

ANIDULAFUNGIN ACCORD may be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Paediatric population

Treatment with ANIDULAFUNGIN ACCORD in neonates (< 1 month old) is not recommended. Treating neonates requires consideration for coverage of disseminated candidiasis including central nervous system (CNS); nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration, resulting in higher doses of polysorbate 80, a formulation excipient. High doses of polysorbates have been associated with potentially life-threatening toxicities in neonates as reported in the literature.

There is no clinical data to support the efficacy and safety of higher doses of anidulafungin than recommended in 4.2.

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.

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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.

No studies have been conducted to evaluate interaction of anidulafungin with other medicines used for the treatment of TB or HIV.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Effective contraception should be used in women of childbearing age while taking ANIDULAFUNGIN ACCORD and for two weeks after discontinuation of treatment.

Pregnancy

Safety in pregnancy and lactation has not been established.

Use of ANIDULAFUNGIN ACCORD should be avoided in pregnant women and women likely to become pregnant unless no safer treatment option is available.

Breast-feeding

It is unknown whether anidulafungin is excreted in human milk. Use of ANIDULAFUNGIN ACCORD should be avoided in women who are breastfeeding their babies.

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In animal studies, anidulafungin was excreted in breastmilk in rats and found to cause foetal harm in rabbits.

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

Side effects such as visual disturbances and central nervous system effects may impair the ability to drive or to use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Infusion-related adverse reactions have been reported with anidulafungin, including rash, pruritus dyspnoea, bronchospasm, hypotension, flushing, hot flush and urticaria.

b. Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	**INCIDENCE**	**ADVERSE REACTION**
Infections and infestations	Less frequent	Fungaemia, candidiasis, pseudomembranous colitis, oral candidiasis, lymphangitis
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, coagulopathy
	Less frequent	Thrombocythaemia, leucopenia, neutropenia, anaemia

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Immune system disorders	Frequency unknown	Anaphylactic shock, anaphylactic reaction*
Metabolism and nutrition disorders	Frequent	Hyperkalaemia, hypokalaemia, hypomagnesaemia
	Less frequent	Hyperglycaemia, hypercalcaemia, Hypernatraemia, hyperuricaemia, hypoalbuminaemia, hypophosphataemia
Psychiatric disorders	Less frequent	Anxiety, delirium, confusional state, auditory hallucination
Nervous system disorders	Frequent	Convulsion, headache
	Less frequent	Dizziness, paraesthesia, central pontine myelinolysis, dysgeusia, Guillain-Barré syndrome, tremor
Eye disorders	Less frequent	Eye pain, visual disturbance, blurred vision, altered visual depth perception
Ear and labyrinth disorders	Less frequent	Unilateral deafness
Cardiac disorders	Less frequent	Atrial fibrillation, sinus dysrhythmia, ventricular extrasystoles, bundle branch block right
Vascular disorders	Frequent	Flushing
	Less frequent	Hot flush, thrombosis, phlebitis, superficial thrombophlebitis, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	Bronchospasm, Dyspnoea

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Gastrointestinal disorders	Frequent	Diarrhoea
	Less frequent	Abdominal pain upper, faecal incontinence, constipation, dyspepsia, dry mouth, oesophageal ulcer, nausea, vomiting
Hepatobiliary disorders	Frequent	Increased gamma- glutamyl transferase, increased blood alkaline phosphatase, increased aspartate aminotransferase, increased alanine aminotransferase
	Less frequent	Abnormal liver function test, cholestasis, increased hepatic enzyme, increased transaminases, hepatic necrosis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
	Less frequent	Urticaria, generalised pruritus, angioedema, hyperhidrosis
Musculoskeletal and connective tissue disorders	Less frequent	Back pain, myalgia, monoarthritis
Renal and urinary disorders	Less frequent	Renal failure, haematuria
General disorders and administration site conditions	Less frequent	Infusion site pain, pyrexia, chills, peripheral oedema

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Investigations	Frequent	Increased blood bilirubin, decreased platelet count, increased blood creatinine, prolonged electrocardiogram QT
	Less frequent	Increased blood amylase, decreased blood magnesium, decreased blood potassium, abnormal electrocardiogram, increased lipase, increased platelet count, increased blood urea, Increased blood creatine phosphokinase, increased blood lactate dehydrogenase, decreased lymphocyte count

***** 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse drug reaction and quality problem reporting form**", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

4.9 Overdose

General supportive measures should be utilised as necessary. In case of overdose, adverse reactions may occur as mentioned in section 4.8. Side effects may be exacerbated or exaggerated in overdose.

ANIDULAFUNGIN ACCORD 100 mg is not dialysable.

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Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use. ATC code: JO2AX06

Mechanism of action

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

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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

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 (0,5-1 hour) and a volume of distribution, 30-50 L, which is similar to total body fluid volume. Anidulafungin is extensively bound (>99 %) to

human plasma proteins. No specific tissue distribution studies of anidulafungin have been done in humans. Therefore, no information is available about the penetration of anidulafungin into the cerebrospinal fluid (CSF) and/or across the blood-brain barrier.

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 characterizes the majority of the plasma concentration-time profile, and a terminal half-life of 40-50 hours that characterises the terminal elimination phase of the profile.

In a single-dose clinical study, radiolabelled (^{14}C) 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 compound. 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 medicine-derived radioactivity were recovered in blood, urine, and faeces 8 weeks post-dose.

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Linearity

Anidulafungin displays linear pharmacokinetics across a wide range of once daily doses (15-130 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 1,1mg/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.

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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

The pharmacokinetics of anidulafungin after at least 5 daily doses were investigated in 24 immunocompromised paediatric (2 to 11 years old) and adolescent (12 to 17 years old) patients with neutropenia. Steady state was achieved on the first day after a loading dose (twice the maintenance dose), and steady state C_{max} and AUC_{ss} increase in a dose-proportional manner. Systemic exposure following daily maintenance dose of 0,75 and 1,5 mg/kg/day in this population were comparable to those observed in adults following 50 and 100 mg/day, respectively. Both regimens were well-tolerated by these patients.

The pharmacokinetics of anidulafungin was investigated in 66 paediatric patients (1 month to < 18 years) with ICC in a prospective, open-label, non-comparative paediatric study following administration of 3,0 mg/kg loading dose and 1,5mg/kg/day maintenance dose (see section 5.1). Based on population pharmacokinetic analysis of

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combined data from adult and paediatric patients with ICC, the mean exposure parameters ($AUC_{0-24,ss}$ and $C_{min,ss}$) at steady state in the overall paediatric patients across age groups (1 month to < 2 years, 2 to < 5 years, and 5 to < 18 years) were comparable to those in adults receiving 200 mg loading dose and 100 mg/day maintenance dose. Body weight adjusted CL (L/h/kg) and volume of distribution at steady state (L/kg) were similar across the age groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fructose

Mannitol

Polysorbate 80

(S)-Lactic acid

Hydrochloric acid,Concentrated (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

36 months

Reconstituted solution:

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 utilized for up to 24 hours when stored at 25 °C.

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Infusion solution:

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 utilized for up to 48 hours from preparation when stored at 25 °C.

6.4 Special precautions for storage

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

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

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

6.5 Nature and contents of container

30 mL type I colourless glass vial with bromobutyl rubber stopper and aluminium flip-off cap with plastic button

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution

ANIDULAFUNGIN ACCORD must be reconstituted with water for injections and subsequently diluted with ONLY sodium chloride 9 mg/mL (0,9 %) solution for injection or 50 mg/mL (5 %) glucose forinfusion. The compatibility of reconstituted Anidulafungin 100 mg Powder for Concentrate for Solution for Infusion with intravenous substances, additives, or medicines other than 9 mg/mL (0,9 %) sodium chloride for infusion or 50 mg/mL (5 %) glucose for infusion has not been established.

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Aseptically reconstitute each vial with addition of 30 mL water for injections and shake carefully to provide a concentration of 3,33 mg/mL. The reconstitution time can be up to 5 mins. After subsequent dilution, the solution is to be discarded if particulate matter or discoloration is identified.

Dilution and infusion

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either particulate matter or discolouration are identified, discard the solution. The infusion solution must not be frozen.

Adult patients

Aseptically transfer the contents of the reconstituted vial(s) into an intravenous bag (or bottle) containing either 9 mg/mL (0,9 %) sodium chloride for infusion or 50 mg/mL (5 %) glucose for infusion obtaining an anidulafungin concentration of 0,77 mg/mL. The table below provides the volumes required for each dose.

Dilution requirements for Anidulafungin 100mg Powder for Concentrate for Solution for Infusion administration.

Dose	**Number of vials required**	**Total reconstituted volume required**	**Infusion volume[A]**	**Total infusion volume[B]**	**Rate of infusion**	**Minimum duration**
100 mg	1-100 mg	30 ml	100 ml	130 ml	1,4 ml/min	90 min
200 mg	2-100 mg	60 ml	200 ml	260 ml	1,4 ml/min	180 min

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A: Either 9 mg/mL (0,9 %) sodium chloride for infusion or 50 mg/mL (5 %) glucose for infusion.

B: Solution for infusion concentration is 0,77 mg/mL.

The rate of infusion should not exceed 1,1 mg/min (equivalent to 1,4 mL/min when reconstituted and diluted perinstructions) (see sections 4.2, 4.4 and 4.8).

Paediatric Patients

For paediatric patients aged 1 month to < 18 years, the volume of infusion solution required to deliver the dose will varydepending on the weight of the patient. The reconstituted solution must be further diluted to a concentration of 0,77mg/mL for the final infusion solution. A programmable syringe or infusion pump is recommended.

The rate of infusionshould not exceed 1,1 mg/minute (equivalent to 1,4 mL/minute or 84 mL/hour when reconstituted and diluted per instructions) (see sections 4.2 and 4.4).

1. Calculate patient dose and reconstitute vial(s) required according to reconstitution instructions to provide aconcentration of 3,33 mg/mL (see sections 2 and 4.2)
2. Calculate the volume (mL) of reconstituted anidulafungin required:
    - Volume of anidulafungin (mL) = Dose of anidulafungin (mg) ÷ 3,33 mg/mL
3. Calculate the total volume of dosing solution (mL) required to provide a final concentration of 0,77 mg/mL:
    - Total volume of dosing solution (mL) = Dose of anidulafungin (mg) ÷ 0,77 mg/mL
4. Calculate the volume of diluent [5 % Dextrose Injection, USP or 0,9 % Sodium Chloride Injection, USP (normal saline)]required to prepare the dosing solution:
    - Volume of diluent (mL) = Total volume of dosing solution (mL) – Volume of anidulafungin (mL)

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5. Aseptically transfer the required volumes (mL) of anidulafungin and 5 % Dextrose Injection, USP or 0,9 % Sodium Chloride Injection, USP (normal saline) into an infusion syringe or IV infusion bag needed for administration.

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

For single use only.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2

6 Coombe Place,

Rivonia,

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

54/20.1.7/0378

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 April 2024

10. DATE OF REVISION OF THE TEXT

28 June 2024