SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ERAXIS® 100 mg Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of ERAXIS contains 100 mg anidulafungin.

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

Contains sugar (fructose and mannitol).

Excipients with known effect

Each vial of ERAXIS 100 mg contains about 120 mg fructose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

A white to off-white lyophilised solid in a 30 mL clear glass vial capped with a 20 mm grey stopper and an aluminium seal with a flip off top.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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).

Other special populations

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

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 ERAXIS have not been established in neonates (< 1 month old) (see section 4.4).

Method of administration

For intravenous use.

For instructions on reconstitution and dilution of ERAXIS see section 6.6.

ERAXIS 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 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 ERAXIS 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

- Hypersensitivity to anidulafungin or any of the excipients of ERAXIS listed in section 6.1.
- Hypersensitivity to other medicines of the echinocandin class (e.g. caspofungin).

4.4 Special warnings and precautions for use

Anaphylactic reactions

Anaphylactic reactions, including shock, have been reported with the use of ERAXIS. If these reactions occur, ERAXIS should be discontinued and appropriate treatment administered (see section 4.8).

Infusion-related reactions

Infusion-related adverse events have been reported with ERAXIS, including rash, urticaria, flushing, pruritus, dyspnoea, bronchospasm and hypotension. The infusion rate should not exceed the recommended infusion rate of 1,1 mg/minute.

Hepatic effects

Laboratory abnormalities in liver function tests have been seen in healthy subjects and patients treated with ERAXIS. In some patients with serious underlying medical conditions who were receiving multiple concomitant medicines along with ERAXIS, clinically significant hepatic abnormalities have occurred. Cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported. Patients who develop abnormal liver function tests during ERAXIS therapy should be monitored for evidence of worsening hepatic function and evaluated for continuing ERAXIS therapy. However, if deteriorating hepatic function is persistent, ERAXIS therapy should be withdrawn.

Paediatric population

Treatment with ERAXIS in neonates (< 1 month old) is not recommended. Treating neonates requires consideration for coverage of disseminated candidiasis including central nervous system (CNS); non-clinical infection models indicate that higher doses of ERAXIS 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.

Information about the excipients of ERAXIS

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

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 ERAXIS.

Sodium content

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

ERAXIS 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.

4.5 Interaction with other medicines and other forms of interaction

Ciclosporin (CYP3A4 substrate)

In a study of 12 healthy adult subjects who received 100 mg/day ERAXIS following a 200 mg loading dose alone and in combination with 1,25 mg/kg oral ciclosporin twice daily, the steady state plasma peak concentration (C_{max}) of ERAXIS was not significantly altered by ciclosporin; however, the steady state area under the concentration-time curve (AUC) was increased by 22 %. An *in vitro* study has shown that ERAXIS has no effect on the metabolism of ciclosporin. Adverse events observed in this study were consistent with those observed in other studies where ERAXIS only was administered. No dosage adjustment of either medicine is required when they are co-administered.

Voriconazole (CYP2C19, CYP2C9, CYP3A4 inhibitor and substrate)

In a study of 17 healthy subjects who received 100 mg/day ERAXIS alone following a 200 mg loading dose, 200 mg twice daily oral voriconazole alone following 400 mg twice on the first day as loading doses, and both in combination, the steady state C_{max} and AUC of ERAXIS and voriconazole were not significantly altered by co-administration. No dosage adjustment of either medicine is required when co-administered.

Tacrolimus (CYP3A4 substrate)

In a study of 35 healthy subjects who received a single oral dose of 5 mg tacrolimus alone, 100 mg/day ERAXIS alone following a 200 mg loading dose and both in combination, the steady state C_{max} and AUC of ERAXIS and tacrolimus were not significantly altered by co-administration. No dosage adjustment of either medicine is required when co-administered.

Liposomal amphotericin B

The pharmacokinetics of ERAXIS were examined in 27 patients (100 mg/day ERAXIS) who were co-administered with liposomal amphotericin B (doses up to 5 mg/kg/day). The population pharmacokinetic analysis showed that, the pharmacokinetics of ERAXIS were not significantly altered by co-administration with amphotericin B when compared to data from patients who did not receive amphotericin B. No dosage adjustment of ERAXIS is required.

Rifampicin (potent CYP450 inducer)

The pharmacokinetics of ERAXIS were examined in 27 patients (50 or 75 mg/day ERAXIS) who were co-administered with rifampicin (doses up to 600 mg/day). The population pharmacokinetic analysis showed that when compared to data from patients that did not receive rifampicin, the pharmacokinetics of ERAXIS were not significantly altered by co-administration with rifampicin. No dosage adjustment of ERAXIS is required.

No studies have been conducted to evaluate interaction of ERAXIS 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 ERAXIS and for two weeks after discontinuation of ERAXIS treatment.

Pregnancy

Safety in pregnancy and lactation has not been established.

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

Breastfeeding

It is not known whether ERAXIS is excreted in human breast milk. Use of ERAXIS should be avoided in women who are breastfeeding their babies.

In animal studies, ERAXIS was found to cause foetal harm in rabbits and was excreted in breastmilk in 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

Summary of the safety profile

Nine hundred and twenty-nine (929) patients received intravenous ERAXIS in clinical trials (672 in Phase 2/3 studies and 257 in Phase I studies). Of the 669 Phase 2/3 patients for whom safety data are available, five hundred and five (505) received ERAXIS for ≥ 14 days.

Three studies (one comparative vs fluconazole, 2 non-comparative) assessed the efficacy of ERAXIS (100 mg) in patients with candidaemia and other deep tissue *Candida* infections. In these three studies, a total of 204 patients received ERAXIS, 119 for ≥ 14 days.

The medicine-related adverse events (MedDRA) listed below were reported with frequencies corresponding to Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infusion-related adverse events have been reported with ERAXIS, including rash, urticaria, flushing, pruritus, dyspnoea, and hypotension.

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Uncommon	Fungaemia, candidiasis, pseudomembranous colitis, oral candidiasis
Blood and lymphatic system disorders	Common	Thrombocytopenia, coagulopathy
	Uncommon	Thrombocythaemia
Metabolism and nutrition disorders	Common	Hyperkalaemia, hypokalaemia, hypomagnesaemia
	Uncommon	Hyperglycaemia, hypercalcaemia, hypernatraemia

Nervous system disorders	Common	Convulsion, headache
Eye disorders	Uncommon	Eye pain, visual disturbance, blurred vision
Cardiac disorders	Uncommon	Atrial fibrillation, sinus dysrhythmia, ventricular extrasystoles, bundle branch block right
Vascular disorders	Common	Flushing
	Uncommon	Thrombosis, hypertension, hot flush
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Upper abdominal pain, vomiting, faecal incontinence, nausea, constipation

Hepato-biliary disorders	Common	Increased gamma-glutamyltransferase, increased blood alkaline phosphatase, increased aspartate aminotransferase, increased alanine aminotransferase
	Uncommon	Abnormal liver function test, cholestasis, increased hepatic enzyme, increased transaminases
Skin and subcutaneous tissue disorders	Common	Rash, pruritus
	Uncommon	Urticaria, generalised pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Back pain
General disorders and administration site conditions	Uncommon	Infusion site pain

Investigations	Common	Increased blood bilirubin, decreased platelet count, increased blood creatinine, prolonged electrocardiogram QT
	Uncommon	Increased blood amylase, decreased blood magnesium, decreased blood potassium, abnormal electrocardiogram, increased lipase, increased platelet count, increased blood urea

In the safety assessment of the full Phase 2/3 patient population (N = 669), the following additional adverse events, all uncommon (≥ 1/1 000 to < 1/100), were of note:

MedDRA system organ class	**Side effect**
Infections and infestations	Lymphangitis
Blood and lymphatic system disorders	Neutropenia, leukopenia, anaemia
Metabolism and nutrition disorders	Hyperuricaemia, hypocalcaemia, hyponatraemia, hypoalbuminaemia, hypophosphataemia
Psychiatric disorders	Anxiety, delirium, confusional state, auditory hallucination

Nervous system disorders	Dizziness, paraesthesia, central pontine myelinolysis, dysgeusia, Guillain-Barré syndrome, tremor
Eye disorders	Altered visual depth perception
Ear and labyrinth disorders	Unilateral deafness
Vascular disorders	Phlebitis, superficial thrombophlebitis, hypotension
Gastrointestinal disorders	Dyspepsia, dry mouth, oesophageal ulcer
Hepato-biliary disorders	Hepatic necrosis
Skin and subcutaneous tissue disorders	Angioedema, hyperhidrosis
Musculoskeletal and connective tissue disorders	Myalgia, monoarthritis
Renal and urinary disorders	Renal failure, haematuria
General disorders and administration site conditions	Pyrexia, chills, peripheral oedema, injection site reaction
Investigations	Increased blood creatine phosphokinase, increased blood lactate dehydrogenase, decreased lymphocyte count

Paediatric population

The safety of ERAXIS was investigated in 68 paediatric patients (1 month to < 18 years) with invasive candidiasis, including candidaemia (ICC) in a prospective, open-label, non-comparative paediatric study. The frequencies of certain hepatobiliary adverse events, including increased alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) appeared at a higher frequency (7 – 10 %) in these paediatric patients than has been observed in adults (2 %). Although

chance or differences in underlying disease severity may have contributed, it cannot be excluded that hepatobiliary adverse reactions occur more frequently in paediatric patients compared to adults.

Post-marketing adverse events

Adverse drug reactions reported from post-marketing experiences are included in the table below:

MedDRA system organ class	**Side effect**
Immune system disorders	Anaphylactic shock, anaphylactic reaction
Respiratory, thoracic and mediastinal disorders	Bronchospasm

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. Health care 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

4.9 Overdose

General supportive measures should be utilised as necessary.

In a study of 10 healthy subjects administered a loading dose of 260 mg followed by 130 mg daily, ERAXIS was well tolerated with no dose limiting toxicity; 3 of the 10 subjects experienced transient, asymptomatic transaminase elevations (≤ 3 x ULN).

During a paediatric clinical trial, one patient received two doses of ERAXIS that were 143 % of the expected dose. No clinical adverse reactions were reported.

Side effects may be exacerbated or exaggerated in overdose.

ERAXIS is not dialysable.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.7 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

The pharmacokinetics of anidulafungin have been characterised in healthy subjects, special populations and patients. A low inter-subject variability in systemic exposure (coefficient of variation of approximately 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 distribution half-life (0,5 – 1 hour) and a volume of distribution of 30 – 50 L that 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 – 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 medicine. Less than 1 % of the administered radioactive dose was excreted in the urine.

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.

Linearity

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

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 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.

Special populations

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.

Hepatic insufficiency

Anidulafungin is not hepatically metabolised.

Renal insufficiency

Anidulafungin has negligible renal clearance (< 1 %).

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} increased in a dose-proportional manner.

Systemic exposure following daily maintenance dose of 0,75 mg/kg/day and 1,5 mg/kg/day in this population were comparable to those observed in adults following 50 mg/day and 100 mg/day, respectively. Both regimens were well-tolerated by these patients.

The pharmacokinetics of anidulafungin were 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 1,5 mg/kg/day maintenance dose. Based on population pharmacokinetic analysis of 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

Tartaric acid

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

Reconstituted solution

The reconstituted solution may be stored at temperatures up to 25 °C for up to 24 hours. Do not freeze. 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 up to 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 – 8 °C).

Excursions for up to 96 hours at temperatures up to 25 ºC are permitted, and the powder may be returned to refrigerated storage (2 – 8 ºC) (see section 6.3).

6.5 Nature and contents of container

A carton containing one clear glass vial of ERAXIS 100 mg lyophilised powder for solution for infusion.

6.6 Special precautions for disposal and other handling

Reconstitution

ERAXIS 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 ERAXIS 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.

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

Dilution and infusion

ERAXIS should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If particulate matter or discolouration is identified, discard the solution.

Adult patients

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 ERAXIS concentration. The table below provides the volumes required for each dose.

Dilution requirements for ERAXIS administration

Dose	Number of vials required	Total recon-stituted 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

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

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

Paediatric population

For paediatric patients aged 1 month to < 18 years, the volume of infusion solution required to deliver the dose will vary depending on the weight of the patient. The reconstituted solution must be further diluted to a concentration of 0,77 mg/mL for the final infusion solution. A programmable syringe or infusion pump is recommended. The rate of infusion should 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 a concentration of 3,33 mg/mL (see sections 2 and 4.2)

2. Calculate the volume (mL) of reconstituted ERAXIS required:

- Volume of ERAXIS (mL) = dose of ERAXIS (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 ERAXIS (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 ERAXIS (mL)

5. Aseptically transfer the required volumes (mL) of ERAXIS 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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31 March 2023

Manufacturer: Pharmacia & Upjohn Company LLC, Kalamazoo, USA