▼This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ERAXIS® (ANIDULAFUNGIN) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

Anidulafungin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ERAXIS is a sterile, lyophilised powder for injection that contains 100 mg anidulafungin.

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of invasive candidiasis, including candidaemia in adult and in paediatric patients one month and older (see Section 5.1).

4.2 Dose and Method of Administration

Specimens for *Candida* 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.

For patients with hereditary fructose intolerance (HFI) and all patients under 2 years of age see Section 4.4 Special Warnings and Precautions for Use.

Adult patients

Invasive candidiasis, including candidaemia

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. The duration of treatment should not exceed one month.

Paediatric patients (one month and older)

The recommended dose is 3.0 mg/kg (not to exceed 200 mg) loading dose of anidulafungin on Day 1, followed by 1.5 mg/kg (not to exceed 100 mg) daily dose thereafter. In general,

antifungal therapy should continue for at least 14 days after the last negative culture (defined as the second of two consecutive negative cultures, separated by at least 24 hours, following the last positive culture) and improvement of clinical signs and symptoms of invasive candidiasis including candidaemia (ICC). Switch to an oral antifungal may occur after a minimum of 10 days on anidulafungin intravenous therapy.

The efficacy and safety of anidulafungin has not been established in neonates (less than 1 month) (see Section 4.4).

Preparation of ERAXIS for administration

ERAXIS must not be given by bolus injection.

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 medications other than 9 mg/mL (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion has not been established. The infusion solution must not be frozen.

Reconstitution

Aseptically reconstitute each vial with 30 ml water for injections to provide a concentration of 3.33 mg/mL. The reconstitution time can be up to 5 minutes. The reconstituted solution should be clear and free from visible particulates. After subsequent dilution, the solution is to be discarded if particulate matter or discolouration is identified.

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

Dilution and Infusion

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter or discoloration 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 obtaining an anidulafungin concentration of 0.77 mg/mL. Table 1 below provides the dilution to a concentration of 0.77 mg/mL for the final infusion solution and infusion instructions for each dose.

Table 1. Dilution Requirements for ERAXIS Administration

Dose	Number of vials	Total Reconstituted Volume	Infusion Volume [A]	Total Infusion Volume[B]	Rate of Infusion	Minimum duration of infusion
100 mg	1	30 mL	100 mL	130 mL	1.4 mL/min or 84 mL/ hour	90 min

200 mg	2	60 mL	200 mL	260 mL	1.4 mL/min or 84 mL/ hour	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.

The rate of infusion should not exceed 1.1 mg/minute (equivalent to 1.4 mL/minute or 84mL/hour when reconstituted and diluted per instructions) (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable effects)).

Paediatric Patients

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 Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable effects))

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 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)

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.

ERAXIS powder for injection contains no antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

Special Populations

Renal and hepatic impairment. No dosing adjustments are required for patients with mild, moderate, or severe hepatic impairment. No dosing adjustments are required for patients with any degree of renal insufficiency, including those on dialysis. ERAXIS can be given without regard to the timing of haemodialysis.

Other special populations. No dosing adjustments are required for adult patients based on gender, weight, ethnicity, HIV status or geriatric status.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients.

Hypersensitivity to other medicinal products of the echinocandin class (*e.g.* caspofungin).

4.4 Special Warnings and Precautions for Use

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 (see Section 4.8 Adverse Effects (Undesirable effects)).

Infusion-related reactions

ERAXIS must not be given by bolus injection.

Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritis, dyspnoea, bronchospasm and hypotension. Infusion-related adverse events are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute (see Section 4.2 Dose And Method Of Administration and Section 4.8 Adverse Effects (Undesirable effects)).

Hepatic effects

Laboratory abnormalities in liver function tests have been seen in healthy subjects and patients treated with anidulafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with anidulafungin, clinically significant hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or *hepatic failure have been reported in patients; a causal relationship to anidulafungin has not been established. Patients who develop abnormal liver function tests during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.

Patients with hereditary fructose intolerance

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

A detailed history with regard to HFI symptoms should be taken of each patient prior to being given this medicinal product.

Infants and 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.

Use in the elderly

Refer to Section 5.2 Pharmacokinetics – Special Populations

Paediatric use

Treatment with anidulafungin in neonates (less than 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.

Effects on laboratory tests

No data available

4.5 Interactions with Other Medicines and Other Forms of Interactions

Nonclinical *in vitro* and *in vivo* studies and clinical studies have demonstrated that anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes. Interaction studies have only been performed in adults. Anidulafungin has negligible renal clearance (< 1%). Minimal interactions are expected with the concomitant medications.

In vitro studies showed that anidulafungin is not metabolised by human cytochrome P450 or by isolated human hepatocytes, and anidulafungin does not significantly inhibit the activities of human CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) at clinically relevant concentrations.

No clinically relevant drug-drug interactions were observed with the following drugs likely to be co-administered with anidulafungin.

Cyclosporin (CYP3A4 substrate). No dosage adjustment of either drug is required when they are co-administered. In a study of 12 healthy adult subjects who received 100 mg/day anidulafungin following a 200 mg loading dose alone and in combination with 1.25 mg/kg oral cyclosporin twice daily, the steady state plasma peak concentration (C_{max}) of anidulafungin was not significantly altered by cyclosporin; however the steady state area under the concentration-time curve (AUC) was increased by 22%. An *in vitro* study has shown that anidulafungin has no effect on the metabolism of cyclosporin. Adverse events observed in this study were consistent with those observed in other studies where anidulafungin only was administered.

Voriconazole (CYP2C19, CYP2C9, CYP3A4 inhibitor and substrate). No dosage adjustment of either drug is required when co-administered. In a study of 17 healthy subjects who received 100 mg/day anidulafungin 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 anidulafungin and voriconazole were not significantly altered by co-administration.

Tacrolimus (CYP3A4 substrate). No dosage adjustment of either drug is required when co-administered. In a study of 35 healthy subjects who received a single oral dose of 5 mg tacrolimus alone, 100 mg/day anidulafungin alone following a 200 mg loading dose and both

in combination, the steady state C_{max} and AUC of anidulafungin and tacrolimus were not significantly altered by co-administration.

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

Rifampicin (potent CYP450 inducer). No dosage adjustment of either drug is required when co-administered. The pharmacokinetics of anidulafungin were examined in 27 patients (50 or 75 mg/day anidulafungin) who were co-administered with rifampicin (doses up to 600 mg/day). The population pharmacokinetic analysis showed that when compared to data from patients who did not receive rifampicin, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with rifampicin.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

Anidulafungin produced no adverse effects on fertility in male or female rats at intravenous doses of 20 mg/kg/day (equivalent to 2 times the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area).

Use in pregnancy – Pregnancy Category B3

Anidulafungin should not be taken during pregnancy, unless indicated by your doctor. Effective contraception should be used in women of chilbearing potential. Contact your doctor immediately if you become pregnant while taking anidulafungin.

Embryo-foetal development studies were conducted with doses up to 20 mg/kg/day in rats and rabbits (equivalent to 2 and 4 times, respectively, the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area). Anidulafungin administration resulted in skeletal changes in rat foetuses including incomplete ossification of various bones and wavy, misaligned or misshapen ribs. These changes were not dose-related and were within the range of the laboratory's historical control database. Developmental effects observed in rabbits (slightly reduced foetal weights) occurred in the high dose group, a dose that also produced maternal toxicity. Anidulafungin crossed the placental barrier in rats and was detected in foetal plasma.

Use in lactation

Adequate studies in lactating mothers have not been performed. Anidulafungin should not be administered to lactaing mothers unless recommended by the clinician after considering the benefit of breast feeding to the child.

A study in lactating rats administered up to 20 mg/kg/day showed no adverse effects on the pups. Anidulafungin was exceted in milk and was detectable in the blood of suckling pups.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Fifteen hundred and sixty-five (1565) patients received intravenous anidulafungin in clinical trials (1308 in Phase 2/3 studies and 257 in Phase I studies).

The safety profile of anidulafungin is based on 840 patients with candidaemia/invasive candidiasis receiving the recommended daily dose of 100 mg in 9 studies.Three studies (one comparative *vs.* fluconazole, 2 non-comparative) assessed the efficacy of anidulafungin (100 mg) in patients with candidaemia and other deep tissue *Candida* infections. In these three studies [invasive candidiasis/candidaemia (ICC) database], a total of 204 patients received anidulafungin, 119 for ≥ 14 days. In six additional studies (two comparative vs. caspofungin and four non-comparative), 636 patients including 53 neutropenic patients and 131 patients with deep tissue infection were studied; the mean durations of intravenous treatment in neutropenic patients and patients with deep tissue infection in these studies were 10.0 (range, 1 to 42 days) and 14.0 (range, 1 to 42 days) days, respectively. Adverse events were typically mild to moderate and seldom led to discontinuation.

The following table includes the all-causality adverse events (MedDRA terms) from 840 subjects receiving 100 mg anidulafungin.

Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, *bronchospasm and hypotension (see Section 4.4 Special Warnings and Precautions for Use).

Adverse Drug Reaction Table 2

System Organ Class	Adverse Drug Reactions
Infections and infestations	Clostridium colitis Fungaemia Candidiasis Oral candidiasis
Blood and lymphatic system disorders	Thrombocytopaenia Thrombocythaemia Coagulopathy
Immune system disorders	Anaphylactic shock[*,#] Anaphylactic reaction[*,#]
Metabolism and nutrition disorders	Hypokalaemia Hyperkalemia Hyperglycaemia Hypomagnesaemia Hypercalcaemia Hypernatraemia
Nervous system disorders	Convulsion Headache
Eye disorders	Vision blurred Visual disturbance Eye pain
Cardiac disorders	Atrial fibrillation Ventricular extrasystoles

Adverse Drug Reaction Table 2

System Organ Class	Adverse Drug Reactions
	Sinus arrhythmia Bundle branch block right
Vascular disorders	Thrombosis Hypertension Flushing Hot flush
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Faecal incontinence Diarrhoea Nausea Vomiting Constipation Abdominal pain upper
Hepatobiliary disorders	Cholestasis
Skin and subcutaneous tissue disorders	Urticaria Pruritus generalised Rash Pruritus
Musculoskeletal and connective tissue disorders	Back pain
General disorders and administration site conditions	Infusion site pain
Investigations	Electrocardiogram QT prolonged Electrocardiogram abnormal Blood potassium decreased Platelet count decreased Blood creatinine increased Blood urea increased Blood amylase increased Lipase increased Alanine aminotransferase increased Blood alkaline phosphatase increased Aspartate aminotransferase increased Blood bilirubin increased Liver function test abnormal Blood magnesium decreased Gamma-glutamyltransferase increased Hepatic enzyme increased Transaminases increased Platelet count increased

[*]ADR identified post-marketing.
[#] See section 4.4.

In the safety assessment of the Phase 2/3 patient population (N = 669), the following additional adverse events,), were of note: neutropenia, leukopenia, anaemia, hyperuricaemia, hypocalcaemia, hyponatraemia, hypoalbuminaemia, hypophosphataemia, anxiety, delirium, confusional state, hallucination auditory, dizziness, paraesthesia, central pontine myelinolysis, dysgeusia, Guillain-Barré syndrome, tremor, altered visual depth perception, deafness unilateral, phlebitis, thrombophlebitis superficial, hypotension, lymphangitis, dyspepsia, dry

mouth, oesophageal ulcer, hepatic necrosis, angioneurotic oedema, hyperhidrosis, myalgia, monoarthritis, renal failure, haematuria, pyrexia, chills, oedema peripheral, injection site reaction, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, lymphocyte count decreased.

Paediatric population

The safety of anidulafungin was investigated in 68 paediatric subjects (1 month to <18 years) with invasive candidiasis, including candidaemia (ICC) in a prospective, open-label, non-comparative paediatric study (see Section 5.1). The adverse event profile of these 68 paediatric subjects was similar to that observed in adults with ICC but hepatobiliary adverse events, in particular Alanine aminotransferase (ALT) increased and Aspartate aminotransferase (AST) increased appeared at a higher frequency in these paediatric patients than has been observed in adults. 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.

Risk of Neonatal Toxicity Associated with Polysorbates

ERAXIS contains polysorbate 80, an inactive ingredient. Thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis have been reported in low-birth weight infants receiving high doses of polysorbate. Polysorbate toxicity has not been reported with ERAXIS. ERAXIS is not approved in pediatric patients younger than 1 month of age *[see section 4.1 and 4.2].*Post Marketing Data

Drug-related adverse events (MedDRA terms) from post-marketing reports with frequency not known (cannot be estimated from the available data) are shown below:

Immune system disorders

Not known: Anaphylactic shock, Anaphylactic reaction

Respiratory, thoracic and mediastinal disorders

Not known: Bronchospasm

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

As with any overdose, 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 events were reported. In a study of 10 healthy subjects administered a loading dose of 260 mg followed by 130 mg daily, anidulafungin 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 subject received two doses of anidulafungin that were 143% of the expected dose. No clinical adverse reactions were reported.

Anidulafungin is not dialysable.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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.*

Activity in vitro

Against *Candida* spp. Anidulafungin is active in vitro against *Candida* spp. including *C. albicans, C. glabrata, C.krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. lusitaniae,* and *C. guilliermondii*.

Against *Aspergillus* spp. Anidulafungin is active in vitro against Aspergillus spp including A. fumigatus, A. flavus, A. niger, and A. terreus. Its activity is not affected by resistance to other classes of antifungal agents, in particular fluconazole.

MICs were determined according to the Clinical and Laboratory Standards Institute (CLSI) approved standard reference method M27 for yeasts.

Anidulafungin breakpoints have not been established. The relationship between clinical response and in vitro activity remains to be elucidated. Significant increases in anidulafungin MICs have been observed in the presence of 50% human serum.

There have been reports of Candida isolates with reduced susceptibility to echinocandins including anidulafungin, but the clinical significance of this observation is unknown.

Activity in vivo

Against *Candida* spp. Parenterally administered anidulafungin was effective against *Candida* spp. in immunocompetent and immunocompromised mouse and rabbit models. Anidulafungin treatment prolonged survival and also reduced the organ burden of *Candida* spp.

Experimental infections included disseminated *C. albicans* infection in neutropenic rabbits, oesophageal/oropharyngeal infection of neutropenic rabbits with fluconazole-resistant *C. albicans* and disseminated infection of neutropenic mice with fluconazole-resistant *C. glabrata*.

Against *Aspergillus* spp. Anidulafungin has also demonstrated activity against *Aspergillus fumigatus* in mouse and rabbit infection models.

In combination with other antifungal agents

In vitro studies of anidulafungin in combination with fluconazole, itraconazole and amphotericin B suggest no antagonism of antifungal activity against *Candida* species. The clinical significance of these results is unknown. *In vitro* studies have evaluated the activity of anidulafungin in combination with itraconazole, voriconazole, and amphotericin B against *Aspergillus* spp. The combination of anidulafungin and amphotericin B showed indifference for 16 of 26 isolates, while anidulafungin in combination with either itraconazole or voriconazole showed synergy against 18 of 26 isolates. The clinical significance of these results is unknown.

Mechanism of Resistance

As breakpoints have not been established for any echinocandin, potential resistance may be assumed if there is a significant rise in MICs for an isolate. No increase in anidulafungin MICs was seen in isolates from clinical trials. In addition, resistance was not seen in *in vitro* studies. Among a number of isolates with elevated echinocandin MICs, only two isolates were reported to have an increased anidulafungin MIC, suggesting the lack of complete cross resistance among echinocandins.

Clinical trials

Invasive Candidiasis including Candidaemia

The safety and efficacy of ERAXIS were evaluated in a pivotal, Phase 3, randomised, double-blind, multicentre, multinational study of patients with candidaemia and/or other forms of invasive candidiasis, associated with clinical signs of infection. Patients were randomised to receive once daily ERAXIS (200 mg IV loading dose followed by 100 mg IV maintenance dose) or IV fluconazole (800 mg loading dose followed by 400 mg maintenance dose). Patients were stratified by APACHE II score (≤ 20 and >20) and the presence or absence of neutropenia. Patients with *Candida* endocarditis, osteomyelitis or meningitis, or those with infection due to *C. krusei*, were excluded from the study. Treatment was administered for at least 14 and not more than 42 days. Patients in both study arms were permitted to switch to oral fluconazole after at least 10 days of intravenous therapy, provided that they were able to tolerate oral medication, were afebrile for at least 24 hours, and the most recent blood cultures were negative for *Candida* species.

Patients who received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site before entry into the study (modified intent-to-treat [MITT] population) were included in the primary analysis of global response at the end of IV therapy. A successful global response required clinical improvement and microbiological eradication. Patients were followed for six weeks beyond the end of all therapy.

Two hundred and fifty-six patients (aged 16 to 91 years) were randomised to treatment and received at least one dose of study medication. The median duration of IV therapy was 14 and 11 days in the ERAXIS and fluconazole arms, respectively. For those who received oral fluconazole, the median duration of oral therapy was 7 days for the ERAXIS arm and 5 days for the fluconazole arm.

Two hundred and forty-five patients (127 ERAXIS, 118 fluconazole) met the criteria for inclusion in the MITT population. Of these, 219 patients (116 ERAXIS (91.3%), 103 fluconazole (87.3%)) had candidaemia only; 5.5% patients in the anidulafungin arm and 9.3% patients in the fluconazole arm had infections at other normally sterile sites; finally 3.1% patients in the ERAXIS arm and 3.4% patients in the fluconazole arm had both (candidaemia and infections at other normally sterile sites). Of these, 219 patients (116 ERAXIS, 103 fluconazole) had candidaemia only.

Risk factors for candidaemia among patients in both treatment arms in this study were: presence of a central venous catheter (78%), receipt of broad-spectrum antibiotics (69%), recent surgery (42%), recent hyperalimentation (25%), and underlying malignancy (22%). The most frequent species isolated at baseline was *C. albicans* (61.6%), followed by *C. glabrata* (20.4%), *C. parapsilosis* (11.8%) and *C. tropicalis* (10.6%). The majority (97%) of patients were non-neutropenic (ANC > 500) and 81% had APACHE II scores less than or equal to 20.

At the end of therapy, ERAXIS was superior to fluconazole in the treatment of patients with candidaemia and/or other forms of invasive candidiasis. In the ERAXIS arm, 96 patients (75.6%) had global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (ERAXIS global success rate minus fluconazole global success rate) was 15.4% (95% CI: 3.9, 27.0).

Global success rates in patients with candidaemia and other *Candida* infections are summarised in Table 3. Table 4 presents outcome and mortality data for the MITT population.

Table 3. Efficacy Analysis: Global Success in patients with Candidaemia and other *Candida* infections (MITT Population)

Timepoint	ERAXIS (N=127) n (%)	Fluconazole (N=118) n (%)	Treatment Difference [a], % (95% C.I.)
End of IV Therapy	96 (75.6)	71 (60.2)	15.42 (3.9, 27.0)
End of All Therapy [b]	94 (74.0)	67 (56.8)	17.24 (2.9, 31.6 [c])
2 Week Follow-up	82 (64.6)	58 (49.2)	15.41 (0.4, 30.4 [c])
6 Week Follow-up	71 (55.9)	52 (44.1)	11.84 (-3.4, 27.0 [c])

a Calculated as ERAXIS minus fluconazole

b 33 patients in each study arm (26% -ERAXIS and 28.8 % fluconazole-treated) switched to oral fluconazole after the end of IV therapy.

c 98.3% confidence intervals, adjusted post hoc for multiple comparisons of secondary time points

Table 4. Outcomes & Mortality in Candidaemia and other *Candida* Infections			
	ERAXIS	**Fluconazole**	**Between group difference [a] (95% CI)**
No. of MITT patients	127	118	
Favorable Outcomes (MITT) At End Of IV Therapy			
All MITT patients			
Candidaemia	88/116 (75.9%)	63/103 (61.2%)	14.7 (2.5, 26.9)
Neutropenic	1/2	2/4	-
Non neutropenic	87/114 (76.3%)	61/99 (61.6%)	-
Multiple sites			
Peritoneal fluid/ intra-abdominal abscess	4/6	5/6	-
Blood/ peritoneum (intra-abdominal abscess)	2/2	0/2	-
Blood /bile	-	1/1	-
Blood/renal	-	1/1	-
Pancreas	-	0/3	-
Pelvic abscess	-	1/2	-
Pleural fluid	1/1	-	-
Blood/ pleural fluid	0/1	-	-
Blood/left thigh lesion biopsy	1/1	-	-
Total	8/11 (72.7%)	8/15 (53.3%)	-
Mortality			
Overall study mortality	29/127 (22.8 %)	37/118 (31.4%)	-
Mortality during study therapy	10/127 (7.9%)	17/118 (14.4%)	-
Mortality attributed to *Candida*	2/127 (1.6%)	5/118 (4.2%)	-

[a] Calculated as ERAXIS minus fluconazole

Candida infections in neutropenic patients

The efficacy of anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) in adult neutropenic patients (defined as absolute neutrophil count ≤500 cells/mm^3, WBC ≤500 cells/mm^3 or classified by the investigator as neutropenic at baseline) with microbiologically confirmed invasive candidiasis was assessed in an analysis of pooled data from 5 prospective studies (1 comparative versus caspofungin and 4 open-label, non-comparative). Patients were treated for at least 14 days. In clinically stable patients, a switch to oral azole therapy was permitted after at least 5 to 10 days of treatment with anidulafungin. A total of 46 patients were included in the analysis. The majority of patients had candidaemia only (84.8%; 39/46). The most common pathogens isolated at baseline were *C. tropicalis* (34.8%; 16/46), *C. krusei* (19.6%; 9/46), *C. parapsilosis* (17.4%; 8/46), *C. albicans* (15.2%; 7/46), and *C. glabrata* (15.2%; 7/46). The successful global response rate at End of

Intravenous Treatment (primary endpoint) was 26/46 (56.5%) and End of All Treatment was 24/46 (52.2%). All-cause mortality up to the end of the study (6 Week Follow-up Visit) was 21/46 (45.7%).

The efficacy of anidulafungin in adult neutropenic patients (defined as absolute neutrophil count ≤500 cells/mm^3 at baseline) with invasive candidiasis was assessed in a prospective, double-blind, randomised, controlled trial. Eligible patients received either anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) or caspofungin (70 mg intravenous loading dose followed by 50 mg intravenous daily) (2:1 randomisation). Patients were treated for at least 14 days. In clinically stable patients, a switch to oral azole therapy was permitted after at least 10 days of study treatment. A total of 14 neutropenic patients with microbiologically confirmed invasive candidiasis (MITT population) were enrolled in the study (11 anidulafungin; 3 caspofungin). The majority of patients had candidaemia only. The most common pathogens isolated at baseline were *C. tropicalis* (4 anidulafungin, 0 caspofungin), *C. parapsilosi*s (2 anidulafungin, 1 caspofungin), *C. krusei* (2 anidulafungin, 1 caspofungin), and *C. ciferrii* (2 anidulafungin, 0 caspofungin). The successful global response rate at the End of Intravenous Treatment (primary endpoint) was 8/11 (72.7%) for anidulafungin and 3/3 (100.0%) for caspofungin (difference -27.3, 95% CI -80.9, 40.3); the successful global response rate at the End of All Treatment was 8/11 (72.7%) for anidulafungin and 3/3 (100.0%) for caspofungin (difference -27.3, 95% CI -80.9, 40.3). All-cause mortality up to the 6 Week Follow-Up visit for anidulafungin (MITT population) was 4/11 (36.4%) and 2/3 (66.7%) for caspofungin.

Patients with microbiologically confirmed invasive candidiasis (MITT population) and neutropenia were identified in an analysis of pooled data from 4 similarly designed prospective, open-label, non-comparative studies. The efficacy of anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) was assessed in 35 adult neutropenic patients defined as absolute neutrophil count ≤500 cells/mm^3 or WBC ≤500 cells/mm^3 in 22 patients or classified by the investigator as neutropenic at baseline in 13 patients. All patients were treated for at least 14 days. In clinically stable patients, a switch to oral azole therapy was permitted after at least 5 to 10 days of treatment with anidulafungin. The majority of patients had candidaemia only (85.7%). The most common pathogens isolated at baseline were *C. tropicalis* (12 patients), *C. albicans* (7 patients), *C. glabrata* (7 patients), *C. krusei* (7 patients), and *C. parapsilosis* (6 patients). The successful global response rate at the End of Intravenous Treatment (primary endpoint) was 18/35 (51.4%) and 16/35 (45.7%) at the End of All Treatment. All-cause mortality by Day 28 was 10/35 (28.6%). The successful global response rate at End of Intravenous Treatment and End of All Treatment were both 7/13 (53.8%) in the 13 patients with neutropenia assessed by investigators at baseline.

Deep tissue infections

The efficacy of anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) in adult patients with microbiologically confirmed deep tissue candidiasis was assessed in an analysis of pooled data from 5 prospective studies (1 comparative and 4 open-label). Patients were treated for at least 14 days. In the 4 open-label studies, a switch to oral azole therapy was permitted after at least 5 to 10 days of treatment with anidulafungin. A total of 129 patients were included in the analysis. Twenty one (16.3%) had concomitant candidaemia. The mean APACHE II score was 14.9 (range, 2 – 44). The most common sites of infection included the peritoneal cavity (54.3%; 70 of 129), hepatobiliary tract (7.0%; 9 of

129), pleural cavity (5.4%; 7 of 129) and kidney (3.1%; 4 of 129). The most common pathogens isolated from a deep tissue site at baseline were *C. albicans* (64.3%; 83 of 129), *C. glabrata* (31.0%; 40 of 129), *C. tropicalis* (11.6%; 15 of 129), and *C. krusei* (5.4%; 7 of 129). The successful global response rate at the end of intravenous treatment (primary endpoint) and end of all treatment and all-cause mortality up to the 6 week follow-up visit is shown in Table 5.

Table 5: Rate of Successful Global Response[a] and All-Cause Mortality in Patients with Deep Tissue Candidiasis – Pooled Analysis

	MITT Population n/N (%)
Global Response of Success at EOIVT[b]	
Overall	102/129 (79.1)
Peritoneal cavity	51/70 (72.9)
Hepatobiliary tract	7/9 (77.8)
Pleural cavity	6/7 (85.7)
Kidney	3/4 (75.0)
Global Response of Success at EOT[b]	94/129 (72.9)
All-Cause Mortality	40/129 (31.0)

[a] A successful global response was defined as both clinical and microbiologic success
[b] EOIVT, End of Intravenous Treatment; EOT, End of All Treatment

Paediatric population

A prospective, open-label, non-comparative, multi-national study assessed the safety and efficacy of anidulafungin in 68 paediatric patients aged 1 month to <18 years with invasive candidiasis including candidaemia (ICC). Patients were stratified by age (1 month to <2 years, 2 to <5 years, and 5 to <18 years) and received once daily intravenous anidulafungin (3.0 mg/kg loading dose on Day 1, and 1.5 mg/kg daily maintenance dose thereafter) for up to 35 days followed by an optional switch to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day). Patients were followed at 2 and 6 weeks after end of all treatment (EOT).

Among 68 patients who received anidulafungin, 64 had microbiologically confirmed *Candida* infection and were evaluated for efficacy in the modified intent-to-treat (MITT) population. Overall, 61 patients (92.2%) had *Candida* isolated from blood only. The most commonly isolated pathogens were *C. albicans* (25 [39.1%] patients), followed by *C. parapsilosis* (17 [26.6%] patients), and *C. tropicalis* (9 [14.1%] patients). A successful global response was defined as having both a clinical response of success (cure or improvement) and a microbiological response of success (eradication or presumed eradication). The overall rates of successful global response in the MITT population are presented in Table 6.

Table 6: Summary of Successful Global Response by Age Group, MITT Population

Successful Global Response, n (%)

Timepoint	Global Response	1 month to <2 years (N=16) n (n/N, %)	2 to <5 years (N=18) n (n/N, %)	5 to <18 years (N=30) n (n/N, %)	Overall (N=64) n (n/N, %)
EOIVT	Success	11 (68.8)	14 (77.8)	20 (66.7)	45 (70.3)
	95% CI	(41.3, 89.0)	(52.4, 93.6)	(47.2, 82.7)	(57.6, 81.1)
EOT	Success	11 (68.8)	14 (77.8)	21 (70.0)	46 (71.9)
	95% CI	(41.3, 89.0)	(52.4, 93.6)	(50.6, 85.3)	(59.2, 82.4)
2-week FU	Success	11 (68.8)	13 (72.2)	22 (73.3)	46 (71.9)
	95% CI	(41.3, 89.0)	(46.5, 90.3)	(54.1, 87.7)	(59.2, 82.4)
6-week FU	Success	11 (68.8)	12 (66.7)	20 (66.7)	43 (67.2)
	95% CI	(41.3, 89.0)	(41.0, 86.7)	(47.2, 82.7)	(54.3, 78.4)

95% CI = exact 95% confidence interval for binomial proportions using Clopper-Pearson method; EOIVT = End of Intravenous Treatment; EOT = End of All Treatment; FU = follow-up; MITT = modified intent-to-treat; N = number of subjects in the population; n = number of subjects with responses

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 (0.5-1 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.

Metabolism

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 drugs 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.

Excretion

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, radiolabeled (^{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 drug. 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 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 (15-130 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 1.0 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, drug 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 Status

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

Impairment of Hepatic Function

Anidulafungin is not hepatically metabolised. Anidulafungin pharmacokinetics were examined in a single dose study 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.

Impairment of Renal Function

Anidulafungin has negligible renal clearance (<1%). In a single dose 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 hemodialysis.

Paediatric

The pharmacokinetics of anidulafungin after daily doses were investigated in immunocompromised paediatric (2 through 11 years) and adolescent (12 through 17 years) patients with neutropenia. The steady state was achieved on the first day after administration of the loading dose (twice the maintenance dose), and the C_{max} and AUC_{ss} increased in a dose-proportional manner. Concentrations and exposures following administration of maintenance doses of 0.75 and 1.5 mg/kg/day in this population were similar to those observed in adults following maintenance doses of 50 and 100 mg/day, respectively, as shown in Table 5 (see Section 4.2 Dose And Method Of Administration).

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 1.5 mg/kg/day maintenance dose (see Section 5.1). Based on population pharmacokinetic analysis of combined data from adult and paediatric patients with ICC, the mean exposure parameters ($AUC_{0\text{-}24,ss}$ 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.

Table 7. Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin Once Daily in Paediatric Subjects				
PK Parameter [a]	Anidulafungin IV Dosing Regimen (LD/MD, mg/kg) [b]			
	1.5/0.75		3.0/1.5	
Age Group	2-11 yrs (N = 6)	12-17 yrs (N = 6)	2-11 yrs (N = 6)	12-17 yrs (N = 6)
$C_{max, ss}$ [mg/L]	3.32 (50.0)	4.35 (22.5)	7.57 (34.2)	6.88 (24.3)
AUC_{ss} [mg·h/L]	41.1 (38.4)	56.2 (27.8)	96.1 (39.5)	102.9 (28.2)

[a] Data were collected on Day 5

[b] LD/MD: loading dose/daily maintenance dose

5.3 Preclinical Safety Data

Genotoxicity

Anidulafungin was not genotoxic in the following *in vitro* studies: bacterial reverse mutation assays, a chromosome aberration assay with Chinese hamster ovary cells, and a forward gene mutation assay with mouse lymphoma cells. Anidulafungin was not genotoxic in mice using the *in vivo* micronucleus assay.

Carcinogenicity

Long-term animal carcinogenicity studies of anidulafungin have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Fructose

Mannitol

Polysorbate 80 (250 mg/vial)

Tartaric acid

Hydrochloric acid

Sodium hydroxide

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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

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 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). Do not freeze. Excursions for up to 96 hours at temperatures up to 25ºC are permitted, and the powder can be returned to refrigerated storage.

6.5 Nature and Contents of Container

100 mg lyophile in a 30 mL Type 1 glass vial with an elastomeric stopper and aluminium seal with flip-off cap.

Anidulafungin is supplied as a pack containing 1 vial of powder.

6.6 Special Precautions for Disposal

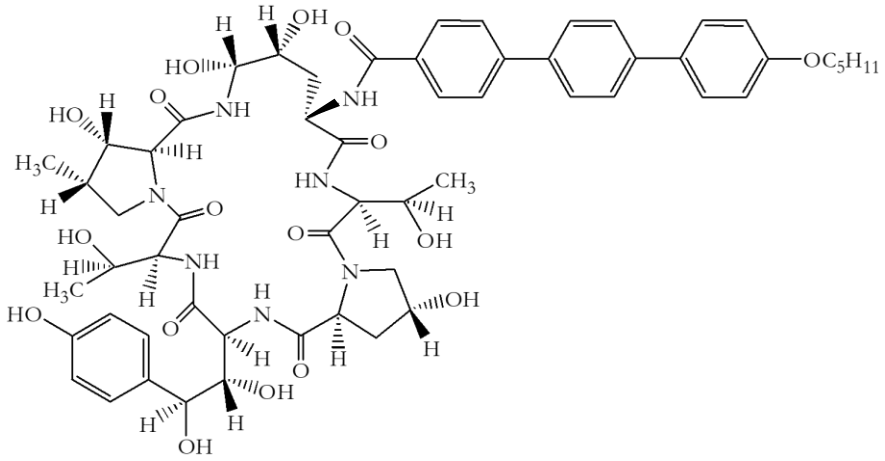
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

ERAXIS (anidulafungin) is a semi-synthetic lipopeptide synthesised from a fermentation product of *Aspergillus nidulans*.

Anidulafungin is a white to off-white powder that is practically insoluble in water and slightly soluble in ethanol.

Chemical structure



Chemical name: 1-[(4R,5R)-4,5-Dihydroxy-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B.

ATC code: JO2 AX 06

The empirical formula of anidulafungin is $C_{58}H_{73}N_7O_{17}$ and the formula weight is 1140.3.

CAS number

166663-25-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

25 March 2009

10. DATE OF REVISION

13 October 2021

ERAXIS® is a registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.1	Addition of paediatric indication to this section
4.2	Dosing information added for paediatric patients Update to storage conditions for reconstituted solution
4.4	Addition of hereditary fructose intolerance warning and precaution in paediatric population
4.8	Addition of adverse effects observed in paediatric patients and neutropenic patients
5.1 and 5.2	Clinical trial information added for paediatric population Clinical trial information added to demonstrate efficacy of anidulafungin in neutropenic patients and patients with deep tissue candidiasis
6.3	Storage conditions for infusion solution and reconstituted solution updated
6.4	Text on allowable temperature excursion added