PRODUCT INFORMATION

ERAXIS® (anidulafungin 100 mg)

Powder for Injection

NAME OF THE MEDICINE

Non-proprietary name: anidulafungin

Chemical name: 1-[(4R,5R)-4,5-Dihydroxy-N^2-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B.

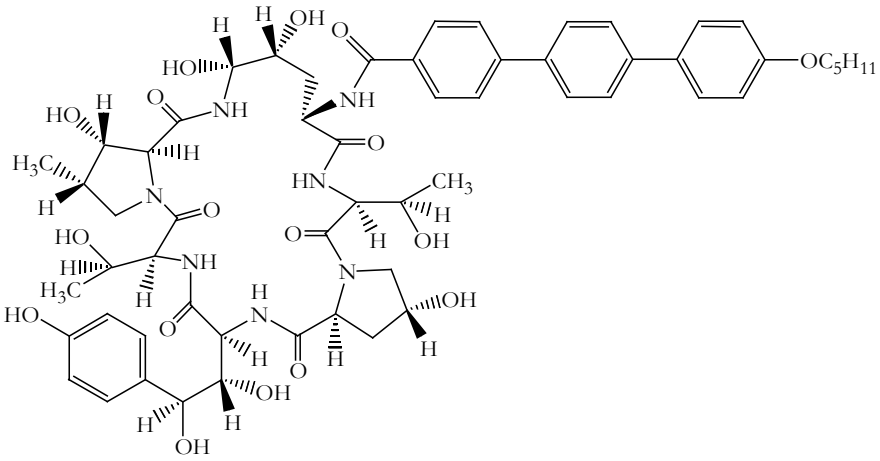
CAS Number: 166663-25-8

ATC code: JO2 AX 06

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

The structural formula is:



DESCRIPTION

Powder for Injection. ERAXIS is a sterile, lyophilised product for injection that contains anidulafungin. In addition to the active ingredient, anidulafungin, ERAXIS contains the following inactive ingredients: fructose, mannitol, polysorbate 80, tartaric acid and may also contain hydrochloric acid and/or sodium hydroxide.

Prior to administration, ERAXIS powder for injection requires reconstitution with water for injections (refer to DOSAGE AND ADMINISTRATION).

PHARMACOLOGY

Microbiology

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.

PHARMACOKINETICS

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.

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 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.

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, 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 $\geq$ 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 1 (refer to DOSAGE AND ADMINISTRATION, Children and adolescents).

Table 1. 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

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 2. Table 3 presents outcome and mortality data for the MITT population.

Table 2. 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 3. 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

INDICATIONS

Treatment of invasive candidiasis, including candidaemia.

CONTRAINDICATIONS

Hypersensitivity to the active substance, or to any of the excipients.
Hypersensitivity to other medicinal products of the echinocandin class (*e.g.* caspofungin).

PRECAUTIONS

The efficacy of ERAXIS in neutropenic patients with candidaemia and in patients with deep tissue *Candida* infections or intra-abdominal abscess and peritonitis has not been established.

*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 ADVERSE 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 DOSAGE AND ADMINISTRATION and ADVERSE 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.

Paediatric Use

Use in patients under 18 years of age is not recommended.

Carcinogenicity

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

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.

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.

Interactions with other medicines

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 cyclosporine. 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.

ADVERSE EFFECTS

Nine hundred and twenty-nine (929) patients received intravenous anidulafungin 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 anidulafungin for ≥ 14 days.

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. Adverse events were typically mild to moderate and seldom led to discontinuation. The drug-related adverse events (MedDRA terms) as compared with fluconazole listed below (Table 4) were reported from this ICC database with frequencies corresponding to Common (≥1/100, ≤1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4. AE Preferred Term		**ICC Integrated Dataset**	
Patients with at least 1 AE		Anidulafungin (N=204)	Fluconazole (N=125)
Common (≥1% to <10%)			
Blood and lymphatic system disorders	Thrombocytopenia	2 (1.0)	0
	Coagulopathy	2 (1.0)	0
Metabolism and nutrition disorders	Hyperkalaemia	2 (1.0)	0
	Hypokalemia	6 (2.9)	3 (2.4)
	Hypomagnesaemia	3 (1.5)	1 (0.8)
Nervous system disorders	Convulsion	3 (1.5)	0
	Headache	2 (1.0)	1 (0.8)
Vascular disorders	Flushing	3 (1.5)	2 (1.6)
Gastrointestinal disorders	Diarrhoea	7 (3.4)	2 (1.6)
Hepatobiliary disorders	Gamma glutamyltransferase increased	2 (1.0)	0
	Blood alkaline phosphotase increased	4 (2.0)	5 (4.0)
	Aspartate aminotransferase increased	2 (1.0)	3 (2.4)
	Alanine aminotransferase increased	4 (2.0)	4 (3.2)
Skin and subcutaneous tissue disorders	Rash	2 (1.0)	1 (0.8)
	Pruritis	2 (1.0)	0

Investigations	Blood bilirubin increased	3 (1.5)	1 (0.8)
	Platelet count decreased	2 (1.0)	0
	Blood creatinine increased	2 (1.0)	0
	Electrocardiogram QT prolonged	2 (1.0)	0

Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, *bronchospasm and hypotension (see PRECAUTIONS).

In the safety assessment of the full Phase 2/3 patient population (N = 669), the following additional adverse events, all uncommon (≥1/1000, <1/100), 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.

***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

DOSAGE AND ADMINISTRATION

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

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.

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.

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.

To reduce microbiological hazard, the reconstituted solution may be held for a maximum of 1 hour and should be stored in a refrigerator (2°C – 8°C). Do not freeze. The reconstituted solution must then be further diluted and this diluted solution must be administered as soon as practicable.

Dilution and Infusion

Aseptically transfer the contents of the reconstituted vial(s) into an IV bag (or bottle) containing either 9 mg/mL (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion obtaining an anidulafungin concentration of 0.77 mg/mL. Table 5 below provides the volumes required for each dose.

Table 5. 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	90 min
200 mg	2	60 mL	200 mL	260 mL	1.4 mL/min	180 min

[A] Either 9 mg/ml (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion.
[B] Infusion solution concentration is 0.77 mg/mL.

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 are identified, discard the solution.

The rate of infusion should not exceed 1.1 mg/minute (equivalent to 1.4 mL/minute when reconstituted and diluted per instructions) (see PRECAUTIONS and ADVERSE EFFECTS).

If not used immediately the infusion solution should be stored in a refrigerator (2°C – 8°C), and should be administered within 24 hours of initial reconstitution. Do not freeze.

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.

Children and adolescents. The experience in children is limited (refer to PHARMACOLOGY, Special populations, Paediatric). Use in patients under 18 years of age is not recommended unless the potential benefit justifies the risk.

OVERDOSAGE

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).

Anidulafungin is not dialysable.

PRESENTATION AND STORAGE CONDITIONS

Powder: 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.

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

POISON SCHEDULE OF THE MEDICINE

S4

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
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TGA APPROVAL DATE:

25 March 2009

Date of most recent amendment: 2 April 2012

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* Please note changes in Product Information