[INTRAVENOUS INFUSION] (not for IV Bolus Injection) **RX ONLY**

**ERAXIS™ (anidulafungin) FOR INJECTION**

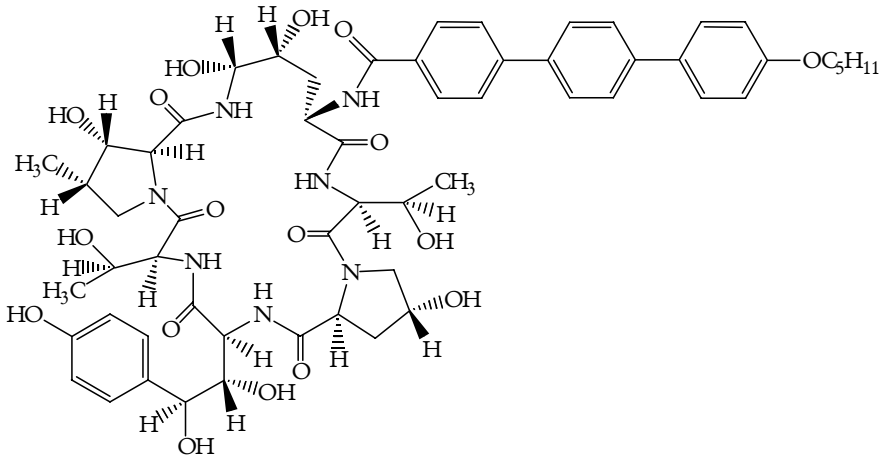
## DESCRIPTION

ERAXIS for Injection is a sterile, lyophilized product for intravenous (IV) infusion that contains anidulafungin. ERAXIS (anidulafungin) is a semi-synthetic lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*. Anidulafungin is an echinocandin, a class of antifungal drugs that inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls.

ERAXIS (anidulafungin) is 1-[(4R,5R)-4,5-Dihydroxy-$N^2$-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B**.** Anidulafungin is a white to off-white powder that is practically insoluble in water and slightly soluble in ethanol. In addition to the active ingredient, anidulafungin, ERAXIS for Injection contains the following inactive ingredients:
*50mg/vial* - fructose (50 mg), mannitol (250 mg), polysorbate 80 (125 mg), tartaric acid (5.6 mg), and sodium hydroxide and/or hydrochloric acid for pH adjustment.
*100mg/vial* - fructose (100 mg), mannitol (500 mg), polysorbate 80 (250 mg), tartaric acid (11.2 mg), and sodium hydroxide and/or hydrochloric acid for pH adjustment.

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

The structural formula is:



Prior to administration, ERAXIS for Injection requires reconstitution with the companion diluent (20% (w/w) Dehydrated Alcohol in Water for Injection) and subsequent dilution with either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline).
DO NOT dilute with other solutions or co-infuse with other medications or electrolytes (see DOSAGE AND ADMINISTRATION).

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

The pharmacokinetics of anidulafungin following IV administration have been characterized in healthy subjects, special populations and patients. Systemic exposures of anidulafungin are dose-proportional and have low intersubject variability (coefficient of variation <25%) as shown in Table 1. The steady state was achieved on the first day after a loading dose (twice the daily maintenance dose) and the estimated plasma accumulation factor at steady state is approximately 2.

**Table 1. Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin Once Daily for 10 Days in Healthy Adult Subjects**

| PK Parameter [a] | Anidulafungin IV Dosing Regimen (LD/MD, mg) [b] | | |
|---|---|---|---|
| | 70/35 [c] [d] (N = 6) | 200/100 (N = 10) | 260/130 [d] [e] (N = 10) |
| $C_{max, ss}$ [mg/L] | 3.55 (13.2) | 8.6 (16.2) | 10.9 (11.7) |
| $AUC_{ss}$ [mg·h/L] | 42.3 (14.5) | 111.8 (24.9) | 168.9 (10.8) |
| CL [L/h] | 0.84 (13.5) | 0.94 (24.0) | 0.78 (11.3) |
| $t_{1/2}$ [h] | 43.2 (17.7) | 52.0 (11.7) | 50.3 (9.7) |

[a] Parameters were obtained from separate studies
[b] LD/MD: loading dose/maintenance dose once daily
[c] Data were collected on Day 7
[d] Safety and efficacy of these doses has not been established
[e] See OVERDOSAGE
$C_{max, ss}$ = the steady state peak concentration
$AUC_{ss}$ = the steady state area under concentration vs. time curve
CL = clearance
$t_{1/2}$ = the terminal elimination half-life

The clearance of anidulafungin is about 1 L/h and anidulafungin has a terminal elimination half-life of 40-50 hours.

### Distribution

The pharmacokinetics of anidulafungin following IV administration are characterized by a short 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 moderately bound to plasma proteins in humans (84%).

**Metabolism**

Hepatic metabolism of anidulafungin has not been observed. Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 (CYP450) isoenzymes. It is unlikely that anidulafungin will have clinically relevant effects on the metabolism of drugs metabolized by CYP450 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 about 24 hours. *In vivo*, the ring-opened product is subsequently converted to peptidic degradants and eliminated.

**Excretion**

In a single-dose clinical study, radiolabeled ($^{14}C$) anidulafungin was administered to healthy subjects. Approximately 30% of the administered radioactive dose was eliminated in the feces 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 feces 8 weeks post-dose.

**Special Populations**

*Patients with fungal infections*

Population pharmacokinetic analyses from four Phase 2/3 clinical studies including 107 male and 118 female patients with fungal infections showed that the pharmacokinetic parameters of anidulafungin are not affected by age, race, or the presence of concomitant medications which are known metabolic substrates, inhibitors or inducers.

The pharmacokinetics of anidulafungin in patients with fungal infections are similar to those observed in healthy subjects. The pharmacokinetic parameters of anidulafungin estimated using population pharmacokinetic modeling following IV administration of a maintenance dose of 50 mg/day or 100 mg/day (following a loading dose) are presented in Table 2.

**Table 2. Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin in Patients with Fungal Infections Estimated Using Population Pharmacokinetic Modeling**

| PK Parameter [a] | Anidulafungin IV Dosing Regimen (LD/MD, mg)[c] | |
|---|---|---|
| | 100/50 | 200/100 |
| Cmax, ss [mg/L] | 4.2 (22.4) | 7.2 (23.3) |
| Cmin, ss [mg/L] | 1.6 (42.1) | 3.3 (41.8) |
| AUCss [mg·h/L] | 55.2 (32.5) | 110.3 (32.5) |
| CL [L/h] | 1.0 (33.5) | |
| t1/2, β [h] [b] | 26.5 (28.5) | |

[a] All the parameters were estimated by population modeling using a two-compartment model with first order elimination; AUCss, Cmax,ss and Cmin,ss (steady state trough plasma concentration) were estimated using individual PK parameters and infusion rate of 1 mg/min to administer recommended doses of 50 and 100 mg/day.
[b] t1/2, β is the predominant elimination half-life that characterizes the majority of the concentration-time profile.
[c] LD/MD: loading dose/daily maintenance dose

*Gender*
Dosage adjustments are not required based on 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.

*Geriatric*
Dosage adjustments are not required for geriatric patients. 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) and the range of clearance was similar.

*Race*
Dosage adjustments are not required based on race. Anidulafungin pharmacokinetics were similar among Whites, Blacks, Asians, and Hispanics.

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

*Hepatic Insufficiency*
Dosage adjustments are not required on the basis of mild, moderate or severe hepatic insufficiency. Anidulafungin is not hepatically metabolized. Anidulafungin pharmacokinetics were examined in subjects with Child-Pugh class A, B or C hepatic insufficiency. Anidulafungin concentrations were not increased in subjects with any degree of hepatic insufficiency. Though a slight decrease in AUC was observed in patients with Child-Pugh C hepatic insufficiency, it was within the range of population estimates noted for healthy subjects.

*Renal Insufficiency*
Dosage adjustments are not required for patients with any degree of renal insufficiency including those on hemodialysis. Anidulafungin has negligible renal clearance. In a clinical study of subjects with mild, moderate, severe or end stage (dialysis-dependent) renal insufficiency, anidulafungin pharmacokinetics were similar to those observed in subjects with normal renal function. Anidulafungin is not dialyzable and may be administered without regard to the timing of hemodialysis.

*Pediatric*
The pharmacokinetics of anidulafungin after daily doses were investigated in immunocompromised pediatric (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 3).(see PRECAUTIONS, Pediatric use)

**Table 3. Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin Once Daily in Pediatric Subjects**

| PK Parameter [a] | Anidulafungin IV Dosing Regimen (LD/MD [b], mg/kg) | | | |
|---|---|---|---|---|
| | 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

## Drug Interaction Studies

*In vitro* studies showed that anidulafungin is not metabolized by human cytochrome P450 or by isolated human hepatocytes, and does not significantly inhibit the activities of clinically important human CYP isoforms (1A2, 2C9, 2D6, 3A4). No clinically relevant drug-drug interactions were observed with drugs likely to be co-administered with anidulafungin.

*Cyclosporine* (CYP3A4 substrate): In a study in which 12 healthy adult subjects received 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose (on Days 1 to 8) and in combination with 1.25 mg/kg oral cyclosporine twice daily (on Days 5 to 8), the steady state $C_{max}$ of anidulafungin was not significantly altered by cyclosporine; the steady state AUC of anidulafungin was increased by 22%. A separate *in vitro* study showed that anidulafungin has no effect on the metabolism of cyclosporine. No dosage adjustment of either drug is warranted when co-administered.

*Voriconazole* (CYP2C19, CYP2C9, CYP3A4 inhibitor and substrate): In a study in which 17 healthy subjects received 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose, 200 mg twice daily oral voriconazole (following two 400 mg loading doses) and both in combination, the steady state $C_{max}$ and AUC of anidulafungin and voriconazole were not significantly altered by co-administration. No dosage adjustment of either drug is warranted when co-administered.

*Tacrolimus* (CYP3A4 substrate): In a study in which 35 healthy subjects received a single oral dose of 5 mg tacrolimus (on Day 1), 100 mg/day maintenance dose of anidulafungin following a

200 mg loading dose (on Days 4 to 12) and both in combination (on Day 13), the steady state $C_{max}$ and AUC of anidulafungin and tacrolimus were not significantly altered by co-administration. No dosage adjustment of either drug is warranted when co-administered.

*AmBisome® (liposomal amphotericin B)*:The pharmacokinetics of anidulafungin were examined in 27 patients that were co-administered liposomal amphotericin B. The population pharmacokinetic analysis showed that when compared to data from patients that did not receive amphotericin B, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with amphotericin B. No dosage adjustment of anidulafungin is warranted.

*Rifampin* (potent CYP450 inducer): The pharmacokinetics of anidulafungin were examined in 27 patients that were co-administered anidulafungin and rifampin. The population pharmacokinetic analysis showed that when compared to data from patients that did not receive rifampin, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with rifampin. No dosage adjustment of anidulafungin is warranted.

## MICROBIOLOGY

### Mechanism of action

Anidulafungin is a semi-synthetic echinocandin with antifungal activity. Anidulafungin inhibits 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.

### Activity *in vitro*

Anidulafungin is active *in vitro* against *Candida albicans*, *C. glabrata*, *C. parapsilosis, and C. tropicalis.* (see INDICATIONS AND USAGE, CLINICAL STUDIES).

MICs were determined according to the Clinical and Laboratory Standards Institute (CLSI) approved standard reference method M27 for susceptibility testing of yeasts. However, no correlation between in vitro activity (MIC) as determined by this method and clinical outcome has been established.

### Activity *in vivo*

Parenterally administered anidulafungin was effective against *Candida albicans* in immunocompetent and immunosuppressed mice and rabbits with disseminated infection as measured by prolonged survival and reduction in mycological burden. Anidulafungin also reduced the mycological burden of fluconazole-resistant *C. albicans* in an oropharyngeal/esophageal infection model in immunosuppressed rabbits.

### Drug Resistance

Emergence of resistance to anidulafungin has not been studied.

Anidulafungin was active against *Candida albicans* resistant to fluconazole. Cross resistance with other echinocandins has not been studied.

## CLINICAL STUDIES

**Candidemia and other *Candida* infections (intra-abdominal abscess, and peritonitis)**
The safety and efficacy of ERAXIS were evaluated in a Phase 3, randomized, double-blind study of patients with candidemia and/or other forms of invasive candidiasis. Patients were randomized to receive once daily IV ERAXIS (200 mg loading dose followed by 100 mg 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 last 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 cure or improvement (significant, but incomplete resolution of signs and symptoms of the *Candida* infection and no additional antifungal treatment), and documented or presumed microbiological eradication. Patients with an indeterminate outcome were analyzed as failures in this population.

Two hundred and fifty-six patients were randomized and received at least one dose of study medication. The median duration of IV therapy was 14 and 11 days in the anidulafungin and fluconazole arms, respectively. For those who received oral fluconazole, the median duration of oral therapy was 7 days for the anidulafungin arm and 5 days for the fluconazole arm.

Patient disposition is presented in Table 4.

**Table 4. Patient Disposition and Reasons for Discontinuation in Candidemia and other *Candida* infection study**

| | Anidulafungin | Fluconazole |
|---|---|---|
| | n (%) | n (%) |
| Treated patients | 131 | 125 |
| Patients completing study through 6 week follow-up | 94 (71.8) | 80 (64.0) |
| **Discontinuations from Study Medication** | | |
| Total discontinued from study medication | 34 (26.0) | 48 (38.4) |
| Discontinued due to adverse events | 12 (9.2) | 21 (16.8) |
| Discontinued due to lack of efficacy | 11 (8.4) | 16 (12.8) |

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, 103 fluconazole) had candidemia only. Risk factors for candidemia 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.

Global success rates in patients with candidemia and other *Candida* infections are summarized in Table 5.

**Table 5. Efficacy Analysis: Global Success in patients with Candidemia 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 [c] (2.9, 31.6) |
| 2 Week Follow-up | 82 (64.6) | 58 (49.2) | 15.41 [c] (0.4, 30.4) |
| 6 Week Follow-up | 71 (55.9) | 52 (44.1) | 11.84 [c] (-3.4, 27.0) |

[a] Calculated as ERAXIS minus fluconazole
[b] 33 patients in each study arm (26% anidulafungin- 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 6 presents outcome and mortality data for the MITT population.

| Table 6. Outcomes & Mortality in Candidemia and other *Candida* Infections | | | |
|---|---|---|---|
| | **Anidulafungin** | **Fluconazole** | **Between group difference [a] ( 95% CI)** |
| **No. of MITT patients** | 127 | 118 | |
| **Favorable Outcomes (MITT) At End Of IV Therapy** | | | |
| **All MITT patients** | | | |
| **Candidemia** | 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

**Esophageal Candidiasis**
ERAXIS was evaluated in a double-blind, double-dummy, randomized Phase 3 study. Three hundred patients received ERAXIS (100 mg loading dose IV on Day 1 followed by 50 mg/day IV) and 301 received oral fluconazole (200 mg loading dose on Day 1 followed by 100 mg/day). Treatment duration was 7 days beyond resolution of symptoms for a minimum of 14 and a maximum of 21 days.

Of the 442 patients with culture confirmed esophageal candidiasis, most patients (91%) had *C. albicans* isolated at the baseline.

Treatment groups were similar in demographic and other baseline characteristics.
In this study, of 280 patients tested, 237 (84.6%) tested HIV positive. In both groups the median time to resolution of symptoms was 5 days and the median duration of therapy was 14 days.

The primary endpoint was endoscopic outcome at end of therapy (EOT). Patients were considered clinically evaluable if they received at least 10 days of therapy, had an EOT assessment with a clinical outcome other than 'indeterminate', had an endoscopy at EOT, and did not have any protocol violations prior to the EOT visit that would affect an assessment of efficacy.

An endoscopic success, defined as cure (endoscopic grade of 0 on a 4 point severity scale) or improvement (decrease of one or more grades from baseline), was seen in 225/231 (97.4%) anidulafungin-treated patients and 233/236 (98.7%) fluconazole-treated patients (Table 7). The majority of these patients were endoscopic cures (grade=0). Two weeks after completing therapy, the anidulafungin group had significantly more endoscopically-documented relapses than the fluconazole group, 120/225 (53.3%) vs. 45/233 (19.3%), respectively (Table 7).

**Table 7. Endoscopy Results in Patients with Esophageal Candidiasis (Clinically Evaluable Population)**

**Endoscopic Response at End of Therapy**

| **Response** | **Anidulafungin N= 231** | **Fluconazole N= 236** | **Treatment Difference** [a] | **95% CI** |
|---|---|---|---|---|
| Endoscopic Success n, (%) | 225 (97.4) | 233 (98.7) | -1.3% | -3.8%, 1.2% |
| Cure | 204 (88.3) | 221 (93.6) | | |
| Improvement | 21 (9.1) | 12 (5.1) | | |
| Failure n, (%) | 6 (2.6) | 3 (1.3) | | |

**Endoscopic Relapse Rates at Follow-up, 2 Weeks Post-Treatment**

| | **Anidulafungin** | **Fluconazole** | **Treatment Difference (%)** [a] | **95% CI** |
|---|---|---|---|---|
| Endoscopic Relapse, n/N (%) | 120/225 (53.3%) | 45/233 (19.3%) | 34.0% | 25.8%, 42.3% |

[a] Calculated as ERAXIS minus fluconazole

Clinical success (cure of and improvement in clinical symptoms including odynophagia/dysphagia and retrosternal pain) occurred in 229/231 (99.1%) of the anidulafungin treated patients and 235/236 (99.6%) of the fluconazole-treated patients at the end of therapy. For patients with *C. albicans*, microbiological success occurred in 142/162 (87.7%) of the anidulafungin-treated group and 157/166 (94.6%) of the fluconazole-treated group at the end of therapy. For patients with *Candida* species other than *C. albicans*, success occurred in 10/12 (83.3%) of the anidulafungin-treated group and 14/16 (87.5%) of the fluconazole-treated group.

## INDICATIONS AND USAGE

ERAXIS is indicated for use in the treatment of the following fungal infections:

Candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis) (see CLINICAL STUDIES and MICROBIOLOGY).
ERAXIS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*, and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group.

Esophageal candidiasis (see CLINICAL STUDIES, Table 7 for higher relapse rates off anidulafungin therapy)

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.

## CONTRAINDICATIONS

ERAXIS is contraindicated in persons with known hypersensitivity to anidulafungin, any component of ERAXIS, or other echinocandins.

## PRECAUTIONS

### Hepatic Effects

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

### Drug Interactions

Pre-clinical *in vitro* and *in vivo* and clinical studies demonstrated that anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes. Anidulafungin has negligible renal clearance. Minimal interactions are expected from the concomitant medications. (see CLINICAL PHARMACOLOGY –Drug Interaction Studies)

Drug interaction studies were performed with anidulafungin and other drugs likely to be co-administered. When used in therapeutic doses, no dosage adjustment of either drug is recommended when anidulafungin is co-administered with voriconazole or tacrolimus, and no dosage adjustment for anidulafungin is recommended when co-administered with amphotericin B or rifampin. (see CLINICAL PHARMACOLOGY –Drug Interaction Studies)

Co-administration with cyclosporine slightly increased the steady state AUC of anidulafungin by 22%. A separate *in vitro* study showed that anidulafungin has no effect on the metabolism of cyclosporine. Adverse events observed in the study were consistent with adverse events observed from other studies with the administration of anidulafungin alone. No dosage adjustment of either drug is warranted for patients on concomitant cyclosporine. (see CLINICAL PHARMACOLOGY –Drug Interaction Studies)

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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.

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).

**Pregnancy**

*Pregnancy Category C*

Embryo-fetal 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 fetuses 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 fetal 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 fetal plasma.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ERAXIS should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

**Nursing Mothers**

ERAXIS should be administered to nursing mothers only if the potential benefit justifies the risk. Anidulafungin was found in the milk of lactating rats. It is not known whether anidulafungin is excreted in human milk.

**Pediatric Use**
Safety and effectiveness of anidulafungin in pediatric patients has not been established. (see CLINICAL PHARMACOLOGY-Special Populations/Pediatric)

## ADVERSE REACTIONS

**General**
Possible histamine-mediated symptoms have been reported with ERAXIS, including rash, urticaria, flushing, pruritus, dyspnea, and hypotension. These events are infrequent when the rate of ERAXIS infusion does not exceed 1.1 mg/minute.

**Overall ERAXIS Safety Experience**
The safety of ERAXIS for Injection was assessed in 929 individuals, including 672 patients in clinical studies and 257 individuals in Phase 1 studies. A total of 633 patients received ERAXIS at daily doses of either 50 or 100 mg. A total of 481 patients received ERAXIS for ≥14 days.

**Candidemia/other *Candida* Infections**
Three studies (one comparative vs. fluconazole, two non-comparative) assessed the efficacy and safety of ERAXIS (100 mg) in patients with candidemia and other *Candida* infections. Table 8 presents treatment-related adverse events that were reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy in the comparative candidemia study.

| **Table 8. Treatment-related [a] adverse events reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia/other *Candida* infections** | | |
|---|---|---|
| | Anidulafungin<br>100 mg [b]<br>N = 131 | Fluconazole<br>400 mg [b]<br>N = 125 |
| | N (%) | N (%) |
| **Subjects with at least 1 treatment-related AE** | 32 (24.4) | 33 (26.4) |
| | | |
| **Gastrointestinal System** | | |
| Diarrhea | 4 (3.1) | 2 (1.6) |
| **Investigations** | | |
| ALT ↑ | 3 (2.3) | 4 (3.2) |
| AST ↑ | 1 (0.8) | 3 (2.4) |
| Alkaline phosphatase ↑ | 2 (1.5) | 5 (4.0) |
| Hepatic enzyme ↑ | 2 (1.5) | 9 (7.2) |
| **Metabolic and Nutritional Systems** | | |
| Hypokalemia | 4 (3.1) | 3 (2.4) |
| **Vascular System** | | |
| Deep vein thrombosis | 1 (0.8) | 3 (2.4) |

[a] Treatment-related AEs are defined as those that are possibly or probably related to study treatment, as determined by the investigator.
[b] Maintenance dose

**Esophageal Candidiasis**

A single phase 3, randomized, double-blind study compared the efficacy and safety of ERAXIS to that of fluconazole in patients with esophageal candidiasis. Table 9 presents treatment-related adverse events that were reported in ≥1.0% of subjects receiving ERAXIS therapy. (No adverse events were reported at a frequency of 2% or greater in patients with esophageal candidiasis).

| **Table 9. Treatment-related[a] adverse events reported in ≥1.0% of subjects receiving ERAXIS or fluconazole therapy for esophageal candidiasis** | | |
|---|---|---|
| | Anidulafungin 50 mg [b] N = 300 | Fluconazole 100 mg [b] N = 301 |
| | N (%) | N (%) |
| **Subjects with at least 1 treatment-related AE** | 43 (14.3) | 50 (16.6) |
| **Blood and lymphatic System** | | |
| Neutropenia | 3 (1.0) | -- |
| Leukopenia | 2 (0.7) | 4 (1.3) |
| **Gastrointestinal System** | | |
| Dyspepsia aggravated | 1 (0.3) | 3 (1.0) |
| Nausea | 3 (1.0) | 3 (1.0) |
| Vomiting NOS | 2 (0.7) | 3 (1.0) |
| **General Disorders and Administration Site Conditions** | | |
| Pyrexia | 2 (0.7) | 3 (1.0) |
| **Investigations** | | |
| Gamma-glutamyl transferase ↑ | 4 (1.3) | 4 (1.3) |
| ALT ↑ | -- | 3 (1.0) |
| AST ↑ | 1 (0.3) | 7 (2.3) |
| **Nervous System** | | |
| Headache | 4 (1.3) | 3 (1.0) |
| **Skin and Subcutaneous Tissue** | | |
| Rash | 3 (1.0) | 2 (0.7) |
| **Vascular System** | | |
| Phlebitis NOS[c] | 2 (0.7) | 4 (1.3) |

[a]Treatment-related AEs include those that are of possible, probable, or unknown relationship to study treatment, as determined by the investigator.
[b] Maintenance dose
[c] Not Otherwise Specified

The following events occurred in either < 2% of patients treated for candidemia/other *Candida* infections, or in < 1% of patients treated for esophageal candidiasis and were judged by investigators to be at least possibly related to ERAXIS:

*Blood and Lymphatic*: coagulopathy, thrombocytopenia
*Cardiac*: atrial fibrillation, bundle branch block (right), sinus arrhythmia, ventricular extrasystoles
*Eye*: eye pain, vision blurred, visual disturbance

*Gastrointestinal*: abdominal pain upper, constipation, diarrhea NOS, dyspepsia, fecal incontinence, nausea, vomiting
*General and Administration Site*: infusion related reaction, peripheral edema, rigors
*Hepatobiliary*: abnormal liver function tests NOS, cholestasis, hepatic necrosis
*Infections*: candidiasis, clostridial infection, fungemia, oral candidiasis
*Investigations*: amylase ↑, bilirubin ↑, CPK ↑, creatinine ↑, electrocardiogram QT prolonged, gamma-glutamyl, electrocardiogram early transition, transferase ↑, lipase ↑, magnesium ↓, platelet count ↑, platelet count ↓, potassium ↓, prothrombin time prolonged, urea ↑
*Metabolism and Nutrition*: hypercalcemia, hyperglycemia, hyperkalemia, hypernatremia, hypomagnesemia
*Musculoskeletal and Connective Tissue*: back pain
*Nervous System*: convulsion, dizziness, headache
*Respiratory, Thoracic and Mediastinal*: cough
*Skin and Subcutaneous Tissue*: angioneurotic edema, erythema, pruritis, pruritis generalized, sweating increased, urticaria, urticaria NOS
*Vascular*: flushing, hot flushes, hypertension, hypotension, thrombophlebitis superficial

## OVERDOSAGE

During clinical trials a single 400 mg dose of ERAXIS 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, ERAXIS was generally well tolerated; 3 of the 10 subjects experienced transient, asymptomatic transaminase elevations (≤3 x ULN).

Anidulafungin is not dialyzable.

The maximum non-lethal dose of anidulafungin in rats was 50 mg/kg, a dose which is equivalent to 10 times the recommended daily dose for esophageal candidiasis (50mg/day) or equivalent to 5 times the recommended daily dose for candidemia and other *Candida* infections (100mg/day), based on relative body surface area comparison.

## ANIMAL PHARMACOLOGY AND TOXICOLOGY

In 3 month studies, liver toxicity, including single cell hepatocellular necrosis, hepatocellular hypertrophy and increased liver weights were observed in monkeys and rats at doses equivalent to 5-6 times human exposure. For both species, hepatocellular hypertrophy was still noted one month after the end of dosing.

## DOSAGE AND ADMINISTRATION

**Candidemia and other Candida infections (intra-abdominal abscess, and peritonitis)**
The recommended dose is a single 200 mg loading dose of ERAXIS on Day 1, followed by 100 mg daily dose 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.

**Esophageal candidiasis**
The recommended dose is a single 100 mg loading dose of ERAXIS on Day 1, followed by 50 mg daily dose thereafter. Patients should be treated for a minimum of 14 days and for at least 7 days following resolution of symptoms. Duration of treatment should be based on the patient's clinical response. Because of the risk of relapse of esophageal candidiasis in patients with HIV infections, suppressive antifungal therapy may be considered after a course of treatment.

No dosing adjustments are required for patients with any degree of renal or hepatic insufficiency, patients using concomitant medications or those in other special populations. (see CLINICAL PHARMACOLOGY – Special Populations and Drug Interaction Studies).

**Preparation of ERAXIS for Administration**
ERAXIS for Injection must be reconstituted with the companion diluent (20% (w/w) Dehydrated Alcohol in Water for Injection) and subsequently diluted with only 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline). The compatibility of reconstituted ERAXIS with intravenous substances, additives, or medications other than 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline) has not been established.

*Reconstitution 50mg/vial*
Aseptically reconstitute each 50 mg vial with 15 mL of the companion diluent (20% (w/w) Dehydrated Alcohol in Water for Injection) to provide a concentration of 3.33 mg/mL. The reconstituted solution should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature). Do not freeze. The reconstituted solution must be further diluted and administered within 24 hours.

*Reconstitution 100mg/vial*
Aseptically reconstitute each 100 mg vial with 30 mL of the companion diluent (20% (w/w) Dehydrated Alcohol in Water for Injection) to provide a concentration of 3.33 mg/mL. The reconstituted solution should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature). Do not freeze. The reconstituted solution must be further diluted and administered within 24 hours.

*Dilution and Infusion*
Aseptically transfer the contents of the reconstituted vial(s) into the appropriately sized IV bag (or bottle) containing either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection,

USP (normal saline). Table 10 provides the number of Unit Packs (ERAXIS vial and companion diluent vial, see HOW SUPPLIED) , volumes and infusion solution concentration for each dose.

**Table 10. Dilution requirements for ERAXIS Administration**

| Dose | Number of Unit Packs Required | Total Reconstituted Volume Required | Infusion Volume [a] | Total Infusion Volume | Infusion Solution Concentration |
|---|---|---|---|---|---|
| 50 mg | 1-50 mg | 15 mL | 100 mL | 115 mL | 0.43 mg/mL |
| 100 mg | 2-50 mg OR 1-100 mg | 30 mL | 250 mL | 280 mL | 0.36 mg/mL |
| 200 mg | 4-50 mg OR 2-100 mg | 60 mL | 500 mL | 560 mL | 0.36 mg/mL |

[a] Either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline)

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.**

The infusion solution should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature). Do not freeze.

## HOW SUPPLIED

ERAXIS (anidulafungin) for Injection, is supplied in a single-use vial of sterile, lyophilized, preservative-free, powder. The companion single-use diluent vial contains 20% (w/w) Dehydrated Alcohol in Water for Injection. ERAXIS (anidulafungin) is available in the following packaging configuration:

**Single Use Unit Pack (containing ERAXIS 50 mg vial and 15 mL Diluent vial)**
NDC 0049-1010-28 One - 50 mg vial and 15 mL diluent vial

**Single Use Unit Pack (containing ERAXIS 100 mg vial and 30 mL Diluent vial)**
NDC 0049-0115-28 One - 100 mg vial and 30 mL diluent vial

## STORAGE

**Unreconstituted vials**
ERAXIS for Injection unreconstituted vials and companion diluent vials should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature). Do not freeze.

**Reconstituted vials**
Reconstituted ERAXIS for Injection should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature). Do not freeze. The reconstituted vials must be further diluted and administered within 24 hours.

**Diluted Product**
Diluted ERAXIS for Injection should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature). Do not freeze.

**Rx only**

Distributed by:
Roerig
Division of Pfizer Inc, NY, NY 10017.

LAB-0336-XX Issued 2006

# 1 Vial Eraxis 100 mg/1 Vial Diluent 30 mL
# IFC

## ELECTRONIC SUBMISSION

FPO: 128C 33% x 14mm

LOT
EXP

IMPRINT AREA
Reads this way

Eraxis™
(anidulafungin)
FOR INJECTION

100 mg

10-6873-00-0

Unit Pack Contains:
1 Sterile Single-use Vial Eraxis™ 100 mg
1 Sterile Single-use Vial Diluent 30 mL

**Eraxis™**
(anidulafungin)
FOR INJECTION

**For Intravenous Infusion Only**
after reconstitution and further dilution

**100 mg**

Package also contains Sterile
Single-use Vial Diluent 20%
(w/w) Dehydrated Alcohol
in Water for Injection (30 mL)

**Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F) [see USP Controlled Room Temperature]. Do not freeze.**

Package Contains 1 Vial each of:
**Eraxis™ (anidulafungin) for Injection (100 mg)**
This single-use vial contains 100 mg anidulafungin, fructose (100 mg), mannitol (500 mg), polysorbate 80 (250 mg), tartaric acid (11.2 mg), and sodium hydroxide and/or hydrochloric acid for pH adjustment.
**Diluent**
This single-use vial contains 30 mL of diluent [20% (w/w) Dehydrated Alcohol in Water for Injection].

**RECONSTITUTION: Eraxis™ must be reconstituted with 30 mL supplied diluent. Each mL contains 3.3 mg anidulafungin (100 mg/30 mL). Further dilute with only 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline) prior to I.V. infusion.**

**DOSAGE AND USE:** See accompanying prescribing information for appropriate dilution of reconstituted solution and storage conditions.

The rate of infusion should not exceed 1.1 mg/minute.

Reconstituted and diluted solutions should be used within 24 hours.

Discard unused portion of Eraxis™ and Diluent.

Eraxis™ is a trademark of
Vicuron Pharmaceuticals Inc.,
a Pfizer Company.

0153

FPO: UPC 85% x 0.31

N
3 0049 – 0115 – 28 5

Unit Pack Contains:
1 Sterile Single-use Vial Eraxis™ 100 mg
1 Sterile Single-use Vial Diluent 30 mL

**Eraxis™**
(anidulafungin)
FOR INJECTION

**For Intravenous Infusion Only**
after reconstitution and further dilution

**100 mg**

Package also contains Sterile
Single-use Vial Diluent 20%
(w/w) Dehydrated Alcohol
in Water for Injection (30 mL)

008202-00

**Rx only** NDC 0049-0115-28

Unit Pack Contains:
1 Sterile Single-use Vial Eraxis™ 100 mg
1 Sterile Single-use Vial Diluent 30 mL

**Eraxis™**
(anidulafungin)
FOR INJECTION

**For Intravenous Infusion Only**
after reconstitution and further dilution

**100 mg**

Package also contains Sterile
Single-use Vial Diluent 20%
(w/w) Dehydrated Alcohol
in Water for Injection (30 mL)

*Distributed by:*
Pfizer
Roerig
Division of Pfizer Inc, NY, NY 10017

**100 mg**

# Sterile Diluent for Eraxis 30 mL

# ELECTRONIC SUBMISSION

LOT/EXP

05687432 0

**Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F) [see USP Controlled Room Temperature]. Do not freeze.**

**DOSAGE AND USE:** See accompanying prescribing information for appropriate dilution of reconstituted solution and storage conditions.

For Eraxis™ Reconstitution Use Only

Pfizer

*Distributed by:*

**Roerig**

Division of Pfizer Inc, NY, NY 10017

**30 mL Single-use Vial** **Rx only**

**Sterile Diluent for Eraxis™**

20% (w/w) Dehydrated Alcohol in Water for Injection

**30 mL**

**Diluent to be used with Eraxis™ (anidulafungin) 100 mg.**

NDC 0049-1110-30-2

CPI-NDSN PRINT LENGTH

# ERAXIS 100 mg - Trade
# IC Label

# ELECTRONIC SUBMISSION

LOT/EXP

05687332 0

**Store at 25°C (77°F) (see insert). Do not freeze.**

**RECONSTITUTION: Eraxis™ must be reconstituted with 30 mL supplied diluent. Each mL contains 3.3 mg anidulafungin (100 mg/30 mL). Further dilute with only 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline) prior to I.V. infusion.**

**DOSAGE AND USE:** See accompanying prescribing information for appropriate dilution of reconstituted solution and storage conditions.

Reconstituted and diluted solutions should be used within 24 hours.

**1 Sterile Single-use Vial** **Rx only**

**Eraxis™**
(anidulafungin)
FOR INJECTION

**For Intravenous Infusion Only**
after reconstitution and further dilution

**100 mg**

Pfizer

*Distributed by:*
**Roerig**
Division of Pfizer Inc, NY, NY 10017

NDC 0013-0040-01 15-80-3

PFIZER INSTITUTIONAL