PRODUCT MONOGRAPH

PrERAXIS®

Anidulafungin For Injection
100 mg / Vial

Antifungal Agent

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Kirkland, Quebec
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Date of Revision:
30 April 2012

Submission Control No: 153866

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PrERAXIS®

anidulafungin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Intravenous infusion	Each active vial contains anidulafungin 100 mg for reconstitution with Water for Injection. The reconstituted solution contains 3.33 mg/mL anidulafungin and the 130 mL infusion solution contains 0.77 mg/mL anidulafungin.	Fructose

** For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ERAXIS (anidulafungin) is indicated for:

- treatment of invasive candidiasis/candidemia in adult non-neutropenic patients.

ERAXIS has not been studied in endocarditis, osteomyelitis, or meningitis due to *Candida*. Infections caused by *C. krusei* have not been studied. Neutropenic patients have not been studied in sufficient numbers to determine the efficacy of the drug in this group (see **CLINICAL TRIALS**).

CONTRAINDICATIONS

ERAXIS is contraindicated to patients with known hypersensitivity to anidulafungin, any component of ERAXIS, or other echinocandins. For a complete listing see the Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General
Patients with rare hereditary problems of fructose intolerance should not take this medicine**.**

Infusion Related
Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, bronchospasm and hypotension. Infusion-related events are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute (see **ADVERSE REACTIONS**, **Adverse Drug Reaction Overview).**

Carcinogenesis and Mutagenesis
No long - term studies in animals have been performed to evaluate the carcinogenic potential of anidulafungin. For information on animal data, see the **DETAILED PHARMACOLOGY** and **TOXICOLOGY** sections of the Product Monograph.

Hepatic
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.

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.

Special Populations

Pregnant Women: Animal studies have shown no selective reproductive toxicity (see **TOXICOLOGY**). There are no adequate and well-controlled studies in pregnant women. Therefore, ERAXIS (anidulafungin) should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Nursing Women: Animal studies have shown excretion of anidulafungin in breast milk (see **TOXICOLOGY**). It is not known whether anidulafungin is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with anidulafungin should be made taking into account the benefit of breast-feeding to the child and the benefit of anidulafungin to the woman.

Pediatrics: The experience in children is limited. Use in patients under 18 years of age is not recommended until further data become available, unless the potential benefit justifies the risk (see **DOSAGE and ADMINISTRATION**, **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Nine hundred and twenty-nine (929) patients received intravenous anidulafungin in clinical trials (672 in Phase 2/3 studies and 257 in Phase 1 studies). Of the 669 Phase 2/3 patients for whom safety data are available, 505 received anidulafungin for ≥ 14 days.

Three studies (one comparative vs fluconazole, two non-comparative) assessed the efficacy of anidulafungin (100 mg) in patients with candidemia 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.

Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, bronchospasm and hypotension. These events can be minimized by infusing anidulafungin at a rate that does not exceed 1.1 mg/minute.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following table presents drug-related adverse events (MedDRA terms) from the ICC database, that were reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia/other *Candida* infections in the comparative study.

Table 1. Drug-related [a] adverse events reported in ≥ 2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia/other *Candida* infections.

Preferred Term	**ERAXIS 100 mg [b] (N = 131)**	**Fluconazole 400 mg [b] (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

Less Common Clinical Trial Adverse Drug Reactions

The drug-related adverse events (MedDRA terms) listed below were reported from the ICC database, with frequencies of ≤1.0% in patients receiving ERAXIS therapy for candidemia/other *Candida* infections in the comparative study (N=131), and from clinical trial post-marketing reports with frequency not known (cannot be estimated from the available data).

Cardiac Disorders: Atrial fibrillation, bundle branch block right, sinus arrhythmia, ventricular extrasystoles

Eye Disorders: Vision blurred, eye pain, visual disturbance

Gastrointestinal Disorders: Nausea, abdominal pain upper, fecal incontinence, loose stools

Hepatobiliary Disorders: Cholestasis

Infections and Infestations: Candidiasis, clostridial infection, oral candidiasis

Investigations: AST ↑, blood amylase ↑, blood creatinine ↑, lipase ↑

Metabolism and Nutrition Disorders: Hyperkalemia, hypercalcemia, hypernatremia

Nervous System Disorders: Headache, convulsion

Skin and Subcutaneous Tissue Disorders: Rash, pruritis generalized, rash papular, urticaria

Social Circumstances: Early adult transition

Vascular Disorders: Deep vein thrombosis, hot flush, hypertension

Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm

Abnormal Hematologic Findings

The following potentially clinically-significant changes from baseline in hematology values were reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia/other *Candida* infections in the comparative study.

Table 2. Potentially Clinically-Significant Changes from Baseline in Hematology Values in ≥2.0% of Subjects receiving ERAXIS or fluconazole therapy for Candidemia/other *Candida* infections.

Parameter (Criteria as fold change)	ERAXIS 100mg[a] (N=131) n (%)			Fluconazole 400mg[a] (N=125) n (%)		
	On-therapy	EIV	6w FU	On-therapy	EIV	6w FU
Bands	**N=55**	**N=56**	**N=39**	**N=49**	**N=56**	**N=28**
Increase (2.0)	2 (3.6)	2 (3.6)	0	2 (4.1)	3 (5.4)	2 (7.1)
Decrease (0.75)	3 (5.5)	2 (3.6)	3 (7.7)	4 (8.2)	1 (1.8)	1 (3.6)
Basophils	**N=90**	**N=100**	**N=63**	**N=79**	**N=97**	**N=48**
Increase (2.0)	0	0	0	0	0	1 (2.1)
Decrease (0.75)	3 (3.3)	1 (1.0)	0	0	0	0
Eosinophils	**N=94**	**N=103**	**N=66**	**N=80**	**N=98**	**N=49**
Increase (4.0)	3 (3.2)	3 (2.9)	5 (7.6)	7 (8.8)	4 (4.1)	3 (6.1)
Hematocrit	**N=105**	**N=119**	**N=74**	**N=84**	**N=107**	**N=58**
Increase (1.4)	6 (5.7)	2 (1.7)	5 (6.8)	2 (2.4)	4 (3.7)	1 (1.7)
Decrease (0.25)	7 (6.7)	3 (2.5)	5 (6.8)	5 (6.0)	2 (1.9)	2 (3.4)
Hemoglobin	**N=105**	**N=119**	**N=74**	**N=85**	**N=107**	**N=58**
Increase (1.4)	4 (3.8)	3 (2.5)	5 (6.8)	3 (3.5)	4 (3.7)	3 (5.2)
Decrease (0.25)	8 (7.6)	3 (2.5)	5 (6.8)	4 (4.7)	2 (1.9)	2 (3.4)
Lymphocytes	**N=99**	**N=105**	**N=69**	**N=82**	**N=99**	**N=50**
Increase (2.0)	27(27.3)	22(21.0)	17(24.6)	19(23.2)	20(20.2)	7 (14.0)
Decrease (0.75)	4 (4.0)	3 (2.9)	0	2 (2.4)	6 (6.1)	0
Monocytes	**N=98**	**N=105**	**N=67**	**N=82**	**N=99**	**N=50**
Increase (2.0)	6 (6.1)	2 (1.9)	3 (4.5)	8 (9.8)	10(10.1)	1 (2.0)
Decrease (0.75)	4 (4.1)	1 (1.0)	1 (1.5)	1 (1.2)	3 (3.0)	1 (2.0)
Neutrophils	**N=99**	**N=105**	**N=68**	**N=82**	**N=99**	**N=50**
Increase (2.0)	3 (3.0)	1 (1.0)	1 (1.5)	0	2 (2.0)	0
Decrease (0.75)	2 (2.0)	0	0	0	0	0
Platelet Count	**N=105**	**N=119**	**N=74**	**N=84**	**N=107**	**N=57**
Increase (2.0)	12(11.4)	11(9.2)	9(12.2)	6(7.1)	11(10.3)	1 (1.8)
Decrease (0.4)	4 (3.8)	4 (3.4)	4 (5.4)	10(11.9)	5 (4.7)	3 (5.3)
WBC	**N=105**	**N=119**	**N=74**	**N=85**	**N=107**	**N=58**
Increase (2.0)	13(12.4)	9 (7.6)	2 (2.7)	5 (5.9)	9 (8.4)	4 (6.9)

EIV=End of IV Therapy; 6w FU=6 week follow-up visit

[a] Maintenance dose

Note: Post baseline potentially clinically-significant change values that are within normal range are not included.

Abnormal Chemistry Findings

The following potentially clinically-significant changes from baseline in chemistry values were reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia/other *Candida* infections in the comparative study.

Table 3. Potentially Clinically-Significant Changes from Baseline in Chemistry Values in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for Candidemia/other *Candida* infections.

Parameter (Criteria as fold change)	ERAXIS 100mg[a] (N=131) n (%)			Fluconazole 400mg[a] (N=125) n (%)		
	On-therapy	EIV	6w FU	On-therapy	EIV	6w FU
Alkaline phosphatase	**N=88**	**N=86**	**N=61**	**N=80**	**N=85**	**N=48**
Increase (2.0)	14(15.9)	14(16.3)	5 (8.2)	12(15.0)	14(16.5)	10(20.8)
ALT	**N=91**	**N=86**	**N=60**	**N=79**	**N=84**	**N=49**
Increase (3.0)	5 (5.5)	5 (5.8)	2 (3.3)	2 (2.5)	6 (7.1)	3 (6.1)
AST	**N=88**	**N=86**	**N=61**	**N=79**	**N=86**	**N=48**
Increase (3.0)	4 (4.5)	1 (1.2)	1 (1.6)	2 (2.5)	7 (8.1)	4 (8.3)
BUN	**N=98**	**N=108**	**N=65**	**N=83**	**N=106**	**N=55**
Increase (3.0)	1 (1.0)	3 (2.8)	3 (4.6)	3 (3.6)	2 (1.9)	0
CO_2	**N=95**	**N=108**	**N=61**	**N=79**	**N=98**	**N=51**
Increase (1.3)	6 (6.3)	6 (5.6)	3 (4.9)	7(8.9)	3 (3.1)	1 (2.0)
Creatinine	**N=104**	**N=114**	**N=71**	**N=85**	**N=108**	**N=56**
Increase (2.0)	3 (2.9)	4 (3.5)	3 (4.2)	2 (2.4)	2 (1.9)	1 (1.8)
Glucose	**N=96**	**N=110**	**N=62**	**N=82**	**N=101**	**N=54**
Increase (3.0)	1 (1.0)	0	2 (3.2)	1 (1.2)	2 (2.0)	2 (3.7)
Decrease (0.4)	6 (6.3)	7 (6.4)	2 (3.2)	6 (7.3)	5 (5.0)	0
Potassium	**N=104**	**N=118**	**N=70**	**N=86**	**N=108**	**N=56**
Increase (1.2)	3 (2.9)	6 (5.1)	1 (1.4)	7 (8.1)	6 (5.6)	2 (3.6)
Decrease (0.15)	14(13.5)	8 (6.8)	3 (4.3)	12(14.0)	7 (6.5)	3 (5.4)
Sodium	**N=103**	**N=118**	**N=70**	**N=86**	**N=109**	**N=56**
Increase (1.1)	3 (2.9)	1 (0.8)	1 (1.4)	3 (3.5)	2 (1.8)	1 (1.8)
Decrease (0.1)	2 (1.9)	2 (1.7)	0	2 (2.3)	1 (0.9)	0
Total bilirubin	**N=86**	**N=84**	**N=58**	**N=79**	**N=88**	**N=47**
Increase (3.0)	4 (4.7)	1 (1.2)	0	2 (2.5)	6 (6.8)	2 (4.3)

EIV=End of IV Therapy; 6w FU=6 week follow-up visit

[a] Maintenance dose *[Missing footnote from NDS]*

Note: Post baseline potentially clinically-significant change values that are within normal range are not included.

Post-Market Adverse Drug Reactions

The following adverse events have been reported during the post-approval period of ERAXIS. Because these reactions are reported voluntarily from populations of uncertain size, it is not always possible to reliably estimate their frequency. A causal relationship to ERAXIS could not be excluded for these adverse events. Adverse events were reported in the following SOC (system organ classes):

Metabolism and Nutrition Disorders (dehydration), Hepatobiliary Disorders (bile duct obstruction), General disorders and administration site conditions (injection site reaction).
Nervous system disorders (cerebrovascular accident, convulsion), Blood and lymphatic system disorders (leucopenia), Investigations (Blood creatinine increased, blood urea increased, tacrolimus drug level decreased, hepatic enzyme increased, liver function test abnormal, white blood cell count decreased). Immune system disorders (Anaphylactic shock, anaphylactic reaction).

DRUG INTERACTIONS

Overview

Preclinical *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 concomitant medications (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

In vitro studies showed that anidulafungin is not metabolized 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. Of note, these *in vitro* studies do not fully exclude possible *in vivo* interactions.

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

Drug-Drug Interactions

Drug interaction studies were performed with anidulafungin and other medicinal products likely to be co-administered (Table 4 and Table 5). Co-administration with cyclosporine increased the steady-state AUC of anidulafungin by 22%, and adverse events observed in the study were consistent with adverse events observed from other studies with the administration of anidulafungin alone. A separate *in vitro* study showed that anidulafungin has no effect on the metabolism of cyclosporine. No dosage adjustment of either drug is recommended when anidulafungin is co-administered with cyclosporine, voriconazole or tacrolimus.

Table 4. Effect of Other Drugs on the Pharmacokinetic Parameters of Anidulafungin

Co-administered Drug	Dose of Co-administered Drug	Dose of Anidulafungin	N	Mean Ratio (90% CI) of Anidulafungin Pharmacokinetic Parameters with/without Co-administered Drug; No Effect = 1.00		
				C_{max}	AUC	Clinical Comment
Cyclosporine	1.25 mg/kg PO BID × 4 days	200 mg IV QD × 1 day, then 100 mg IV QD × 7 days	11	1.08†	1.22†*	No dose adjustment required
Voriconazole	400 mg PO BID × 1 day, then 200 mg PO BID × 3 days	200 mg IV QD × 1 day, then 100 mg IV QD × 3 days	17	1.01 (0.97 to 1.04)	0.97 (0.95 to 1.00)	No dose adjustment required
Tacrolimus	5 mg PO single dose	200 mg IV QD × 1 day, then 100 mg IV QD × 9 days	35	1.03 (1.00 to 1.06)	1.07 (1.05 to 1.09)	No dose adjustment required

† 90% confidence interval not reported
* Statistically significant (p<0.05)

Table 5. Effect of Anidulafungin on the Pharmacokinetic Parameters of Other Drugs

Co-administered Drug	Dose of Co-administered Drug	Dose of Anidulafungin	N	Mean Ratio (90% CI) of Co-administered Drug Pharmacokinetic Parameters with/without Anidulafungin; No Effect = 1.00		
				C_{max}	AUC	Clinical Comment
Voriconazole	400 mg PO BID × 1 day, then 200 mg PO BID × 3 days	200 mg IV QD × 1 day, then 100 mg IV QD × 3 days	17	0.94 (0.89 to 0.98)	0.97 (0.92 to 1.03)	No dose adjustment required
Tacrolimus	5 mg PO single dose	200 mg IV QD × 1 day, then 100 mg IV QD × 9 days	35	0.99 (0.90 to 1.09)	1.02 (0.93 to 1.11)	No dose adjustment required

Other Medications

The pharmacokinetics of anidulafungin were examined in 27 patients that were co-administered with liposomal amphotericin B as well as in 27 patients that were co-administered with rifampin (potent CYP450 inducer). The population pharmacokinetic analysis suggested that when compared to data from patients that did not receive amphotericin B or rifampin, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with amphotericin B or rifampin. No dose adjustment for anidulafungin is recommended when co-administered with amphotericin B or rifampin.

Population pharmacokinetic analysis has shown that the pharmacokinetic parameters of anidulafungin were not affected by the presence of concomitant medications which are known metabolic substrates, inhibitors or inducers of **cytochrome P450 isoenzymes**.

Population pharmacokinetic analysis also indicated that overall healthy subjects, HIV positive subjects, and HIV-positive patients with fungal infections appeared to have comparable exposure parameters.

Drug-Food Interactions

Not applicable since ERAXIS (anidulafungin) is a parenterally administered product.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ERAXIS should be reconstituted with Water for Injection to a concentration of 3.33 mg/mL and subsequently diluted to a concentration of 0.77 mg/mL before use according to the instructions given in section **Reconstitution**.

Recommended Dose and Dosage Adjustment

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.

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.

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. Anidulafungin can be given without regard to the timing of hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Other Special Populations

No dose adjustments are required for adult patients based on patient gender, ethnicity, HIV positivity, or geriatric status. (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Children and Adolescents

The experience in children is limited. Use in patients under 18 years of age is not recommended until further data become available, unless the potential benefit justifies the risk (see **WARNINGS and PRECAUTIONS**, **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Administration

It is recommended that ERAXIS is administered at a maximum rate of infusion that does not exceed 1.1 mg/minute.

Reconstitution:

Anidulafungin must be reconstituted with sterile 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 anidulafungin 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.

Aseptically reconstitute each vial with 30 mL sterile Water for Injection to provide a concentration of 3.33 mg/mL. The reconstitution time can be up to 5 minutes.

If not used immediately, the reconstituted solution should be stored at 15 - 30 °C for up to 24 hours.

Dilution and Infusion
Aseptically transfer the contents of the reconstituted vial(s) into an IV bag (or bottle) containing either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline) obtaining an anidulafungin concentration of 0.77 mg/ml. The table below provides the volumes required for each dose.

Dilution Requirements for Anidulafungin Administration

Dose	Number of vials required	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	260mL	1.4 mL /min	180 min

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

The infusion solution may be stored at 15 - 30 °C for 48 hours or stored frozen for at least 72 hours. The infusion solution must be administered within 24 hours. For single use only.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If particulate matter or discolouration are identified, discard the solution.

For further information on storage and stability for the infusion and reconstituted solution, see section **STORAGE AND STABILITY**.

OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

As with any overdose, general supportive measures should be utilized 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 dialyzable.

The maximum non-lethal single dose of anidulafungin in rats was 50 mg/kg, a dose which is equivalent to 5 times the recommended daily dose in humans for Candidemia and other *Candida* infections [100 mg/day] , based on the relative body surface area comparison.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

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*.

Anidulafungin has *in vitro* activity against various pathogenic fungi of the *Aspergillus* and *Candida* species (see **MICROBIOLOGY)**.

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 6. The steady state was achieved on the first day after a loading dose (twice the daily maintenance dose).

Table 6. 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)	150/75 (N = 9)	200/100 (N = 10)	260/130 [d,e] (N = 10)
$C_{max,ss}$ [mg/L]	3.5 (13.2)	4.9 (20.3)	8.6 (16.2)	10.9 (11.7)
$C_{min,ss}$ [mg/L]	1.2 (12.6)	1.9 (5.7)	3.2 (21.6)	5.2 (12.6)
AUC_{ss} [mg·h/L]	42.3 (14.5)	65.5 (8.8)	111.8 (24.9)	168.9 (10.8)
CL [L/h]	0.84 (13.5)	1.2 (8.5)	0.94 (24.0)	0.78 (11.3)
$t_{1/2}$ [h]	43.2 (17.7)	51.2 (6.9)	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
$C_{min,ss}$ = the steady state trough concentration
AUC_{ss} = the steady state area under concentration vs. time curve
CL = clearance
$t_{1/2}$ = the terminal elimination half-life
CV = coefficient of variation*

The clearance and terminal elimination half-life of anidulafungin are about 1 L/h and 40-50 hours, respectively. Both of these pharmacokinetic parameters have been found to be independent of dosage. The pharmacokinetics of anidulafungin in patients with fungal infections are similar to those observed in healthy subjects (see **Special Populations and Conditions,** Patients with fungal infections).

Distribution: The pharmacokinetics of anidulafungin are characterized 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 metabolized 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: 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 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.

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

Special Populations and Conditions

Patients with fungal infections: Population pharmacokinetic analyses from four Phase 2/3 clinical studies including 107 males 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 of **cytochrome P450 isoenzymes**. 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 7.

Table 7. 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
$C_{max, ss}$ [mg/L]	4.2 (22.4)	7.2 (23.3)
$C_{min, ss}$ [mg/L]	1.6 (42.1)	3.3 (41.8)
AUC_{ss} [mg·h/L]	55.2 (32.5)	110.3 (32.5)
CL [L/h]	1.0 (33.5)	
$t_{1/2, \beta}$ [h][b]	26.5 (28.5)	

[a] All the parameters were estimated by population modeling using a two-compartment model with first order elimination; AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ (steady state trough plasma concentration) were estimated using individual PK parameters and infusion rate of 1 mg/min to administer recommended doses of 50 or 100 mg/day.

[b] $t_{1/2, \beta}$ is the predominant elimination half-life that characterizes the majority of the concentration-time profile.

[c] LD/MD: loading dose/maintenance dose

CV = coefficient of variation*

Pediatrics: The pharmacokinetics of anidulafungin after daily doses were investigated in 24 immunocompromised pediatric (2 to 11 years old) and adolescent (12 to 17 years old) patients with neutropenia. The steady state was achieved on the first day after a loading dose (twice the maintenance dose), and the steady state C_{max} and AUC_{ss} increase in a dose-proportional manner. The systemic exposures following the daily maintenance doses of 0.75 and 1.5 mg/kg/day in patients aged 2 to 17 years old were comparable to those observed in adults following 50 and 100 mg/day, respectively.

Geriatrics: 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.

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.

Ethnicity: Anidulafungin pharmacokinetics were similar among Caucasians, Blacks, Asians, and Hispanics.

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

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. Although slight decrease in AUC was observed in patients with Child-Pugh C hepatic insufficiency, the decrease was within the range of population estimates noted for healthy subjects.

Renal Insufficiency: Anidulafungin has negligible renal clearance (< 1%). In a clinical study of subjects with mild, moderate, severe or end stage (dialysis-dependent) renal insufficiency, anidulafungin pharmacokinetics were similar to those observed in subjects with normal renal function. Anidulafungin is not dialyzable and may be administered without regard to the timing of hemodialysis.

STORAGE AND STABILITY

Unreconstituted Vials:
Unreconstituted vials should be **stored at 2-8ºC**. Excursions for 96 hours up to 25°C are permitted, and the powder can be returned to refrigerated storage.

Reconstituted Solution:
Reconstitute with water for injection. The reconstituted solution may be stored at 15 - 30°C for up to 24 hours. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C.

Infusion Solution:
The infusion solution should be stored at 15 - 30°C, for up to 48 hours or stored frozen for at least 72 hours. Chemical and physical in-use stability of the infusion solution has been demonstrated for 48 hours at 25ºC.

SPECIAL HANDLING INSTRUCTIONS
Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form and Packaging:
ERAXIS (anidulafungin) is marketed as a carton containing 1 vial of 100 mg anidulafungin.

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

Composition:
Anidulafungin powder: Each vial contains 100 mg anidulafungin and the following inactive ingredients: Fructose, mannitol, polysorbate 80, tartaric acid and sodium hydroxide and/or hydrochloric acid for pH adjustment.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

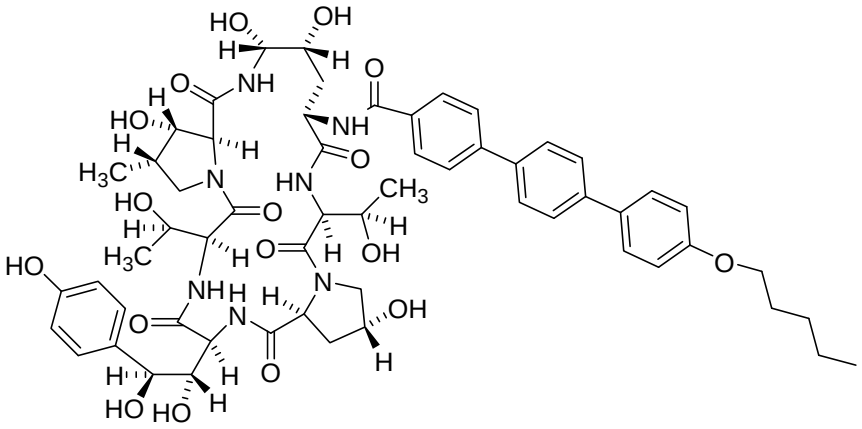
Common name: Anidulafungin

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

Molecular formula: $C_{58}H_{73}N_7O_{17}$

Molecular weight: 1140.2

Structural formula:



Description: Anidulafungin is a white to off-white solid. It is slightly soluble in ethanol, water/acetonitrile (1:1) and is insoluble in water, citrate buffer, acetonitrile and ethanol/water (1:1).

pK_a: 9.5

CLINICAL TRIALS

Study Demographics and Trial Design

Candidemia and Other Forms of Invasive Candidiasis

The safety and efficacy of anidulafungin were evaluated in a pivotal Phase 3, randomized, double-blind, multicentre, multinational study of patients with candidemia and/or other forms of invasive candidiasis, associated with clinical signs of infection. Patients were randomized to receive once daily i.v. anidulafungin (200 mg loading dose followed by 100 mg maintenance dose) or i.v. 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 i.v. therapy. A successful global response required clinical improvement and microbiological eradication. Patients were followed for 6 weeks beyond the end of all therapy.

Two hundred and fifty-six (256) patients (aged 16 to 91 years) were randomized to treatment and received at least one dose of study medication. The median duration of i.v. therapy was 14 and 11 days in the ERAXIS (anidulafungin) 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.

Patient disposition is presented in Table 8.

Table 8. Patient Disposition and Reasons for Discontinuation in Candidemia and Other *Candida* Infection Study

	ERAXIS	**Fluconazole**
	n (%)	n (%)
Treated patients	131	125
Patients completing study through 6-week follow-up[a]	94 (71.8)	80 (64.0)
Discontinuations from Study Medication		
Total discontinued from study medication[b]	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)

[a]: 37 (28.2%) and 45 (36.0%) patients in the ERAXIS and fluconazole groups, respectively, discontinued the study prior to 6-week follow-up.

[b]: 97 (74.0%) and 77 (61.6%) of the patients completed study medication in the ERAXIS and fluconazole groups, respectively.

Two hundred and forty-five (245) patients (127 anidulafungin, 118 fluconazole) met the criteria for inclusion in the MITT population. Of these, 219 patients (116 anidulafungin (91.3%), 103 fluconazole (87.3%)) had candidemia 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 anidulafungin arm and 3.4% patients in the fluconazole arm had both (candidemia and infections at other normally sterile sites). The most frequent species isolated at baseline were *C. albicans* (63.8% anidulafungin, 59.3% fluconazole), followed by *C. glabrata* (15.7%, 25.4%), *C. parapsilosis* (10.2%, 13.6%) and *C. tropicalis* (11.8%, 9.3%).The majority (97%) of patients were non-neutropenic (ANC > 500) and 81% had APACHE II scores less than or equal to 20.

Table 9 presents outcome and mortality data for the MITT population.

Table 9. Outcomes & Mortality in Candidemia and Other *Candida* Infections

	ERAXIS	**Fluconazole**	**Between group difference [a] (95% CI)**
No. of MITT patients	127	118	
Favorable Outcomes (MITT) at End of i.v. 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

Global success rates in patients with candidemia and other *Candida* infections are summarized in Table 10.

Table 10. 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 i.v. 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 i.v.therapy.
[c] 98.3% confidence intervals, adjusted post hoc for multiple comparisons of secondary time points

DETAILED PHARMACOLOGY

Pharmacodynamics

ECG Evaluation
No placebo-controlled, randomized, phase I study with a positive control arm for QT prolongation was performed in order to evaluate the effect of anidulafungin on the QT interval.

In the clinical trials of patients with candidemia and other *Candida* infections, ECGs were evaluated at screening and at post-dose (within 3 hours of drug infusion) on day 3 or on day 6. There were no notable differences between anidulafungin-treated patients and fluconazole-treated patients in the mean change from baseline in QTc interval or in the distribution of patients among QTc interval changes from baseline.

Pharmacokinetics

The relevant human pharmacokinetic data can be found in Sections **ACTION AND CLINICAL PHARMACOLOGY and DRUG INTERACTIONS.**

The oral bioavailability of anidulafungin is very low (2-7%).

No specific tissue distribution study of anidulafungin has been done in humans. The tissue distribution of anidulafungin, however, was evaluated extensively in preclinical species. It has been noted in rat studies that anidulafungin crosses the placenta and can be found in fetal blood, and anidulafungin is secreted in milk. Crossing of the blood-brain barrier was limited in healthy

uninfected rats. However, in rabbits with disseminated candidiasis, anidulafungin has been shown to cross the blood-brain barrier and reduce fungal burden in the brain. At the intravenous dose of 5 mg/kg, maximum concentrations of anidulafungin in rat liver (15.9 mg/kg), spleen (24.2 mg/kg), kidney (16.1 mg/kg), and lung (31.1 mg/kg) were greater than the observed plasma concentration of 5.3 mg/L. Skin (4.0 mg/kg) and muscle (3.8 mg/kg) contained similar levels of anidulafungin as plasma. Anidulafungin is widely distributed in all species with the steady-state volume of distribution approximately equivalent to the total body water.

The disposition of anidulafungin was similar across all species. A clear allometric relationship was observed for anidulafungin clearance across mice, rats, rabbits, dogs, monkeys and humans. Clearance was dependent on the weight of the species such that clearance per kilogram (CL/kg) was similar across species.

Special Populations and Conditions

The relevant human pharmacokinetic data can be found in Sections **ACTION AND CLINICAL PHARMACOLOGY and WARNINGS AND PRECAUTIONS**.

Animal Pharmacology

Studies were conducted to evaluate the effects of ERAXIS on the cardiovascular, respiratory, renal, and central nervous systems in animals following a single IV dose.

Cardiovascular: The potential for anidulafungin to cause hemodynamic or electrocardiographic (ECG) effects in rats and monkeys was evaluated. Administration of ERAXIS to rats resulted in decreased blood pressure during the first hour following dosing (maximum decrease at 10 min after dosing), accompanied by a compensatory increase in heart rate during the first 20 min following dosing (maximum increase at 20 minutes). These effects occurred only in the highest tested dose, providing a clinical margin of exposure approximately 5-fold higher than the human $C_{max,\ ss}$ for the 200/100 mg dosing regimen. The hemodynamic changes observed in rats, and their timecourse, are consistent with histamine-mediated infusion-related reactions that occur in single and repeat-dose studies in rats, but not monkeys, given high doses of ERAXIS.

To further characterize cardiovascular safety, a study in telemetered monkeys was performed. No drug-related effects observed on blood pressure, heart rate, or electrocardiogram interval analyses were observed at the highest dose tested (35 mg/kg), providing a clinical margin of exposure approximately 9-fold the human $C_{max,\ ss}$ for the 200/100 mg dosing regimen.

Central Nervous System: Behavioral pharmacology studies in mice evaluated the potential of ERAXIS to impact several aspects of the CNS including general observations, autonomic function, spontaneous activity, pro- or anticonvulsant activity in response to either electroshock or a drug, enzyme competition/CNS depression, neuromuscular function, sensorimotor reactivity, and analgesic potential. ERAXIS had no effect on any parameter evaluated except analgesic potential. At the highest dose tested, ERAXIS significantly reduced responses suggesting it may have analgesic-like activity at clinically-relevant doses (based on body surface area calculations).

Renal: Following single IV doses of ERAXIS in rats, the following endpoints were evaluated as a measure of renal pharmacology: urine volume, pH, and chloride, as well as urinary and serum concentrations of sodium, potassium, and creatinine, and osmolality (urine and serum). Creatinine clearance and fractional excretion of sodium were also calculated. Following treatment, rats in the highest dose group experienced marked decreases in sodium and chloride excretion, as well as a significant reduction in urine volume. Effects were not observed at lower doses. The effect on chloride, the counter ion, is considered secondary to the effect on sodium. The effects on sodium excretion and urine volume are considered to result from hemodynamic changes that occur in the rat at the same doses. These effects were observed at a dose that provides a clinical margin of exposure approximately 5-fold higher than the human $C_{max,\ ss}$ for the 200/100 mg dosing regimen.

Respiratory: Rats were used as a model to evaluate the potential for ERAXIS to cause respiratory effects using a chamber and pressure transducer system. No effects were observed at any dose tested, providing a clinical margin of exposure at the no observed effect level (NOEL) of approximately 5-fold the human C_{max}, ss for the 200/100 mg dosing regimen.

MICROBIOLOGY

Activity in vitro

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* and *Aspergillus* species 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 Standard Institute (CLSI) approved standard reference method M27 for susceptibility testing of yeasts. The relationship between clinical response and *in vitro* activity remains to be elucidated.

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

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, esophageal/oropharyngeal infection of neutropenic rabbits with fluconazole-resistant *C. albicans* and disseminated infection of neutropenic mice with fluconazole-resistant *C. glabrata.* Anidulafungin has also demonstrated activity against *Aspergillus fumigatus* in mouse and rabbit infection models.

TOXICOLOGY

Acute Toxicity
The acute median lethal dose (LD_{50}) was 71 mg/kg in rats and >100 mg/kg in mice. The maximum non-lethal dose in rats was 50 mg/kg and the minimal lethal dose in this species was 100 mg/kg. A maximum non-lethal dose in mice was not identified as no deaths were observed at the highest dose tested (100 mg/kg).

Repeat Dose Toxicity
Anidulafungin has been evaluated via intravenous infusion in rats and monkeys in repeat dose toxicity studies of 1- and 3-months duration. Additionally, immunotoxicity was assessed after 1 month of dosing (T-dependent antibody response, T-cell receptor-driven proliferation, immunophenotyping).

In 3 month studies, liver toxicity, including single cell hepatocellular necrosis, hepatocellular hypertrophy and increased liver weights accompanied by increases in hepatic enzymes and cholesterol were observed in monkeys and rats at doses equivalent to 4-6 times human exposure. For both species, hepatocellular hypertrophy was still noted one month after the end of dosing.

Rats given high doses of anidulafungin experienced transient infusion-related (histamine-mediated) reactions within the first 10-20 minutes of the infusion or 1 hour after dosing. These were characterized by hemodynamic changes (decreases in blood pressure and increases in heart rate in the safety pharmacology studies) and clinical signs that included ataxia, sternal recumbence, restlessness, red skin and ears, and swollen muzzles. These reactions generally subsided after 1-5 days of dosing. Similar reactions were not reported in monkeys. The occurrence at the first dose and the lack of persistance following repeated dosing argue against an immunogenic/systemic hypersensitivity effect.

Reproductive Toxicology
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).

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 did not produce any drug-related developmental toxicity in rats. Developmental effects observed in rabbits (slightly reduced fetal weights) occurred in the high dose group only, a dose that also produced maternal toxicity.

Anidulafungin crossed the placental barrier in rats and was detected in fetal plasma. Anidulafungin was found in the milk of lactating rats. It is not known whether anidulafungin is excreted in human milk.

Carcinogenicity
No long - term studies in animals have been performed to evaluate the carcinogenic potential of anidulafungin.

Mutagenicity

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.

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PART III: CONSUMER INFORMATION

PRERAXIS®
Anidulafungin

This leaflet is part III of a three-part "Product Monograph" published when ERAXIS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ERAXIS. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your doctor or pharmacist.

- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:
ERAXIS belongs to a group of medicines called echinocandins. These medicines are used to treat serious fungal infections.
ERAXIS is prescribed to treat a type of fungal infection called invasive candidiasis (including candidemia). The infection is caused by fungal cells (yeasts) called *Candida*.

What it does:
Fungal cells exposed to ERAXIS have incomplete or defective cell walls making them fragile or unable to grow, thereby killing the cells and reducing the infection.

When it should not be used:
If you are allergic (hypersensitive) to anidulafungin, other echinocandins, or any of the other ingredients of ERAXIS (Fructose, Mannitol, Polysorbate 80, Tartaric acid, Sodium hydroxide or Hydrochloric acid).

What the medicinal ingredient is:
The active ingredient is anidulafungin.

What the important non-medicinal ingredients are:

Fructose, Mannitol, Polysorbate 80, Tartaric acid, Sodium hydroxide (for pH-adjustment), Hydrochloric acid (for pH-adjustment)

What dosage form it comes in:
ERAXIS is marketed as a carton containing 1 vial of 100 mg powder for solution for infusion.

WARNINGS AND PRECAUTIONS

BEFORE you use ERAXIS talk to your doctor or pharmacist:

- If you have been told by your doctor that you have an intolerance to some sugars. Patients with rare hereditary problems of fructose intolerance should not take this medicine. This medicinal product contains fructose.
- If you become pregnant while taking ERAXIS: ERAXIS should not be taken during pregnancy, unless indicated by your doctor. Effective contraception should be used in women of childbearing potential.
- If you are breast-feeding or planning to breast feed . You and you doctor will decide whether you should take this medication or not while breastfeeding or whether you should discontinue breastfeeding.
- If you have any allergies to this drug or its ingredients or components of the container.
- If you have liver problems.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is not expected that ERAXIS will interact with other medications or that any adjustments will be necessary to other medicines you may be taking. However, do not start or stop any other medications without your doctor or pharmacist's approval.

PROPER USE OF THIS MEDICATION

ERAXIS will always be prepared and given to you by a doctor or a healthcare professional.

Usual adult dose:
ERAXIS should be administered once a day, by slow infusion into your vein over approximately 1.5 to 3 hours. The treatment starts with a loading dose of 200 mg on the first day, then with subsequent daily maintenance dose of 100 mg.

ERAXIS should not be given to patients under 18 years of age.

Your doctor will determine the duration of your treatment and how much anidulafungin you will receive each day, and will monitor your response and condition.

Overdose:
Your doctor will monitor your response and condition to determine what ERAXIS treatment is needed. However, if you are concerned that you may have been given too much ERAXIS, tell your doctor or another healthcare professional immediately.

Missed Dose:
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However tell your doctor or pharmacist if you think that a dose has been forgotten.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ERAXIS can cause side effects, although not everybody gets them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	-Hypokalemia (low potassium levels) and symptoms such as muscle weakness, and cramping, irregular heart beat, frequent urination		✓	
Uncommon	- High blood pressure	✓		
	-Liver problems (hepatitis) with symptoms such as persistent abdominal pain, nausea, Vomiting		✓	✓
	- Anaphylactic (allergic) reactions with symptoms such as rash, hives, low blood pressure, fainting, swelling of mouth, throat and extremities, weakness, difficulty in breathing		✓	

• A common effect is diarrhea.
• Uncommon side effects include headache, rash, itching, flushing, eye pain, infusion site reaction
If these reactions become troublesome, contact your doctor

This is not a complete list of side effects. For any unexpected effects while taking* ERAXIS*, contact your doctor or pharmacist.

HOW TO STORE IT

Unreconstituted vials of ERAXIS are stored in a refrigerator (2-8°C). Do not freeze.

Keep out of the reach and sight of children.
Do not use ERAXIS after the expiry date which is stated on the label.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free to 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffectTM Canada Web site at www.healthcanada.gc.ca/medeffect.

***NOTE:* Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.**

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc., at 1-800-463-6001 (Medical Information).

This leaflet was prepared by Pfizer Canada Inc.

Last revised: 30 April 2012

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