PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ERAXIS®

Anidulafungin For Injection

Powder for solution, 100 mg / Vial, Intravenous

Antifungal Agent

Pfizer Canada ULC

17 300 Trans-Canada Highway

Kirkland, Quebec

H9J 2M5

Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

1 Indication	05/2023
1 Indications, 1.1 Pediatrics	05/2023
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	05/2023
7 Warnings and Precautions, 7.1.3 Pediatrics	05/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ERAXIS (anidulafungin) is indicated for:

- treatment of invasive candidiasis/candidemia in non-neutropenic adult and pediatric patients one month and older (see **14 CLINICAL TRIALS**)

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 **14 CLINICAL TRIALS**).

1.1 Pediatrics

Pediatrics (>1 month and older): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ERAXIS in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see **14 CLINICAL TRIALS**).

Pediatrics (<1 month): The safety and efficacy of ERAXIS in pediatric patients <1 month of age has not been established; therefore, Health Canada has not authorized an indication for use in pediatrics <1 month old.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see section **10.3 Pharmacokinetics, Special Populations and Conditions**).

2 CONTRAINDICATIONS

ERAXIS is contraindicated in patients who are hypersensitive to anidulafungin or to any ingredient in the formulation, including any non-medicinal ingredient or other echinocandins, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**

4.DOSAGE AND ADMINISTRATION

4.1 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 **4.3 Reconstitution**.

4.2 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 **10 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 **10 CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Pediatric patients (one month and older)

Invasive candidiasis, including candidemia

The recommended dose is 3.0 mg/kg (not to exceed 200 mg) loading dose of anidulafungin on Day 1, followed by 1.5 mg/kg (not to exceed 100 mg) daily dose thereafter. In general, antifungal therapy should continue for at least 14 days after the last negative culture (defined as the second of two consecutive negative cultures, separated by at least 24 hours, following the last positive culture) and improvement of clinical signs and symptoms of invasive candidiasis including candidemia (ICC). Switch to an oral antifungal may occur after a minimum of 10 days on anidulafungin intravenous therapy.

The efficacy and safety of anidulafungin has not been established in neonates (less than 1 month) (see section **7 WARNINGS AND PRECAUTIONS**).

4.3 Reconstitution

Parenteral Products:

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. The infusion solution must not be frozen.

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 should be stored at 15 - 30 °C, for up to 48 hours. Do not freeze. 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 **11 STORAGE, STABILITY AND DISPOSAL**.

4.4 Administration

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

5 OVERDOSAGE

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).

During a pediatric clinical trial, one subject received two doses of anidulafungin that were 143% of the expected dose. No clinical adverse reactions were reported.

Anidulafungin is not 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal 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, Mannitol, Polysorbate 80, Tartaric acid, Sodium hydroxide (for pH-adjustment), Hydrochloric acid (for pH-adjustment)

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.

7 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 **8 ADVERSE REACTIONS**,

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 **16 NON-CLINICAL TOXICOLOGY** sections of the Product Monograph.

Hepatic/Biliary/Pancreatic
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.

Immune

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.

7.1 Special Populations

7.1.1 Pregnant Women

Animal studies have shown no selective reproductive toxicity (see **16 NON-CLINICAL 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.

7.1.2 Breast-feeding

Animal studies have shown excretion of anidulafungin in breast milk (see **16 NON-CLINICAL 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.

7.1.3 Pediatrics

The safety and efficacy of ERAXIS have not been established in neonates (less than 1 month of age). Nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration (**16 NON-CLINICAL TOXICOLOGY**), resulting in higher doses of polysorbate 80, a formulation excipient. High doses of polysorbates have been associated with potentially life-threatening toxicities in neonates as reported in the literature. There is no clinical data to support the efficacy and safety of higher doses of anidulafungin than recommended.

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety of anidulafungin was investigated in 68 pediatric subjects (1 month to < 18 years) with invasive candidiasis, including candidemia (ICC) in a prospective, open-label, non-comparative pediatrics study (see section **14 CLINICAL TRIALS**). The adverse event profile of these 68 pediatric subjects was similar to that observed in adults with ICC; however, the frequencies of certain hepatobiliary adverse events, including alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased appeared at a higher frequency (7-10%) in these pediatric patients than has been observed in adults (2%). Although chance or differences in underlying disease severity may have contributed, it cannot be excluded that hepatobiliary adverse reactions occur more frequently in pediatric patients compared to adults.

8.3 Less Common Clinical Trial Adverse Reactions

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial 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

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

8.5 Post-Market Adverse 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)

9 DRUG INTERACTIONS

9.2 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 **10 CLINICAL PHARMACOLOGY**, **10.3 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, 3A3/4) 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.

9.4 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.

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 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**).

10.3 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.

Metabolism: Hepatic metabolism of anidulafungin has not been observed. Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes. It is unlikely that anidulafungin will have clinically relevant effects on the metabolism of drugs 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.

Elimination: 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.

The pharmacokinetics of anidulafungin was investigated in 66 pediatric patients (1 month to <18 years) with ICC in a prospective. open-label, non-comparative pediatric study following administration of 3.0 mg/kg loading dose and 1.5 mg/kg/day maintenance dose (See **Section 14 Clinical Trials**). Based on population pharmacokinetic analysis of combined data from adult and pediatric patients with ICC, the mean exposure parameters ($AUC_{0\text{-}24,\ ss}$ and $C_{min,ss}$) at steady state in the overall pediatric patients across age groups (1 month to <2 years, 2 to <5 years, and 5 to <18 years) were comparable to those in adults receiving 200 mg loading dose and 100 mg/day maintenance dose. Body weight adjusted CL (L/h/kg) and volume of distribution at steady state (L/kg) were similar across the age groups.

- **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.

- **Sex:** 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.

- **Origin:** 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.

11 STORAGE, STABILITY AND DISPOSAL

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

Infusion Solution:
The infusion solution should be stored at 15 - 30°C, for up to 48 hours. Do not freeze.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

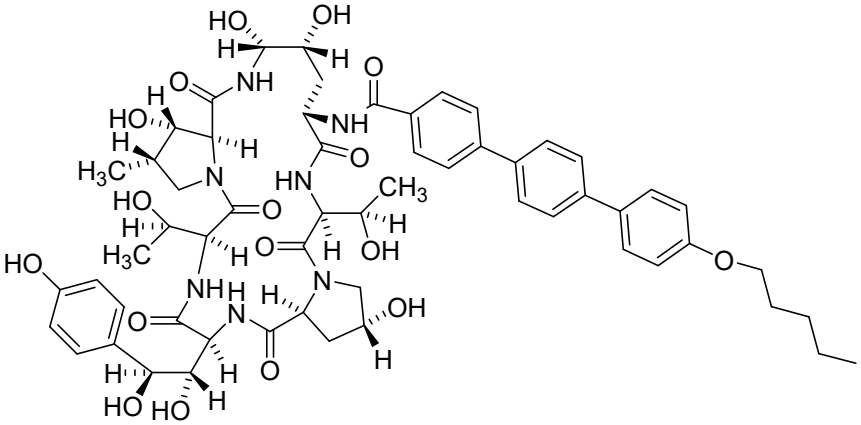
Drug Substance

Proper name: Anidulafungin

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

Molecular formula and molecular mass: C58H73N7O17, 1140.2

Structural formula:



Physicochemical properties:

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

14 CLINICAL TRIALS

Trial Design and Study Demographics

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.

14.2 Study Results

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

Pediatric Population

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

Among 68 patients who received anidulafungin, 64 had microbiologically confirmed *Candida* infection and were evaluated for efficacy in the modified intent-to-treat (MITT) population. Overall, 61 patients (92.2%) had *Candida* isolated from blood only. The most commonly isolated pathogens were *Candida albicans* (25 [39.1%] patients), followed by *Candida parapsilosis* (17 [26.6%] patients), and *Candida tropicalis* (9 [14.1%] patients). A successful global response was defined as having both a clinical response of success (cure or improvement) and a microbiological response of success (eradication or presumed eradication). The overall rates of successful global response in the MITT population are presented in Table 11.

Table 11: Summary of Successful Global Response by Age Group, MITT Population
Successful Global Response, n (%)

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

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

15 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.

16 NON-CLINICAL TOXICOLOGY

General 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.

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

Reproductive and Developmental 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.

Results of pharmacokinetic-pharmacodynamic studies in rabbit models of disseminated candidiasis and hematogenous Candida meningoencephalitis indicated that higher doses of anidulafungin were needed to optimally treat infections of CNS tissues relative to non-CNS tissues.

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.

Juvenile Toxicity
Studies conducted in juvenile rats did not indicate a greater susceptibility to anidulafungin hepatoxicity compared to adult animals at doses up to 4 times human therapeutic exposure.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrERAXIS®

Anidulafungin

Read this carefully before you start taking **ERAXIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ERAXIS**.

What is ERAXIS used for?

- 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*.

How does ERAXIS work?

ERAXIS belongs to a group of medicines called echinocandins. These medicines are used to treat serious fungal infections.

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.

What are the ingredients in ERAXIS?

Medicinal ingredients: anidulafungin

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

ERAXIS comes in the following dosage forms:

ERAXIS is marketed as a carton containing 1 vial of 100 mg powder for solution for infusion.

Do not use ERAXIS if:

- If you are allergic (hypersensitive) to anidulafungin, other echinocandins, or any of the other ingredients of ERAXIS. See “What are the ingredients in ERAXIS?” section, above.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ERAXIS. Talk about any health conditions or problems you may have, including if 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.
- are pregnant or think you might be pregnant while taking ERAXIS. It is not known how ERAXIS will affect your baby. Your healthcare professional will determine if the benefits outweigh the risks for you and your baby. You should use effective contraception while taking ERAXIS.
- 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.

- you have liver problems.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ERAXIS:

- ERAXIS will be prepared and given to you by your healthcare professional.
- ERAXIS is given by slow infusion into your vein over approximately 1.5 to 3 hours.
- Your doctor will determine your dose and how long you should take ERAXIS based on your condition. Overall antifungal treatment should continue for at least 14 days after the last positive test.

Usual dose:

Adults:

- On the first day, you will receive a single dose of 200 mg.
- Each day afterwards, you will receive 100 mg daily.

Children (Older than 1 month old):

- Your child's dose will be determined by their weight.
- On the first day, your child will receive a single dose of 3 mg/kg (up to a maximum dose of 200 mg).
- Each day afterwards, they will receive 1.5 mg/kg daily (up to a maximum dose of 100 mg).

Overdose:

If you think you, or a person you are caring for, have taken too much ERAXIS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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.

What are possible side effects from using ERAXIS?

These are not all the possible side effects you may have when taking ERAXIS. If you experience any side effects not listed here, tell your healthcare professional.

- A common effect is diarrhea.

- Uncommon side effects include headache, rash, itching, flushing, eye pain, infusion site reaction

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypokalemia (low potassium levels) and symptoms such as muscle weakness, and cramping, irregular heartbeat, 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		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Unreconstituted vials of ERAXIS are stored in a refrigerator (2-8°C). Do not freeze.
Reconstituted solution may be stored at 15-30°C for up to 24 hours.
Keep out of reach and sight of children.
Do not use ERAXIS after the expiry date which is stated on the label.

If you want more information about ERAXIS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

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