
Anidulafungin for Injection

ERAXIS[®] Lyophilized Powder for Reconstitution for Infusion



1. GENERIC NAME

Anidulafungin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single use vial containing 100 mg anidulafungin

The reconstituted solution contains 3.33 mg/mL anidulafungin and the diluted solution contains 0.77 mg/mL anidulafungin.

List of Excipients:

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

3. DOSAGE FORM AND STRENGTH

Anidulafungin lyophilized powder for reconstitution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Treatment of invasive candidiasis, including candidemia, in adult patients (see section 5.2).

Treatment of esophageal candidiasis, in adult patients (see section 5.2).

4.2 Posology and Method of Administration

Recommended Dosage in Adults

Candidemia and other *Candida* infections (intra-abdominal abscess and peritonitis)

The recommended dose is a single 200 mg loading dose of anidulafungin on Day 1, followed by a 100 mg once daily maintenance dose thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

Esophageal Candidiasis

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

Preparation for Administration

Anidulafungin for Injection must be reconstituted with sterile Water for Injection and subsequently diluted only with 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline), prior to administration.

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. Do **NOT** dilute with other solutions or co-infuse with other medications or electrolytes. The infusion solution must not be frozen.

Reconstitution of the 100 mg/vial

Aseptically reconstitute each 100 mg vial with 30 mL of sterile Water for Injection to provide a concentration of 3.33 mg/mL.

Storage of the Reconstituted Solution

Anidulafungin reconstituted solution can be stored at 25°C (77°F) for up to 24 hours prior to dilution into the infusion solution. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C (77°F). From a microbiological point of view, following good aseptic practices, the reconstituted solution can be utilized for up to 24 hours when stored at 25°C.

Dilution and Administration of the Infusion

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

Adult Patients

Aseptically transfer the contents of the reconstituted vial(s) into the appropriately sized IV bag (or bottle) containing either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline). See Table 1 for the dilution to a concentration of 0.77 mg/mL for the final infusion solution and infusion instructions for each dose. **The rate of infusion should not exceed 1.1 mg/minute (equivalent to 1.4 mL/minute or 84 mL/hour when reconstituted and diluted per instructions) (see section 4.4).**

Table 1: Dilution Requirements for Anidulafungin Administration

Dose	Number of Vials Required	Total Reconstituted Volume Required	Infusion Volume ^a	Total Infusion Volume ^b	Rate of Infusion	Minimum Duration of Infusion
100 mg	2–50 mg or 1–100 mg	30 mL	100 mL	130 mL	1.4 mL/min or 84 mL/ hour	90 min
200 mg	4–50 mg or 2–100 mg	60 mL	200 mL	260 mL	1.4 mL/min or 84 mL/ hour	180 min

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

^b Infusion solution concentration is 0.77 mg/mL

4.3 Contraindications

Anidulafungin is contraindicated in:

- Patients with known hypersensitivity to anidulafungin, any component of anidulafungin, or other echinocandins (see section 4.4).
- Patients with known or suspected Hereditary Fructose Intolerance (HFI) (see section 4.4).

4.4 Special Warnings and Precautions for Use

Hepatic Adverse Reactions

Laboratory abnormalities in liver tests have been seen in healthy volunteers 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 (see sections 4.8 and 6.1). Patients who develop abnormal liver tests during anidulafungin therapy should be monitored for evidence of worsening hepatic tests and evaluated

for risk/benefit of continuing anidulafungin therapy.

Anaphylactic and Hypersensitivity Reactions

Anaphylactic reactions, including shock, were reported with the use of anidulafungin. If these reactions occur, anidulafungin should be discontinued and appropriate treatment administered. (see section 4.8)

Infusion-related adverse reactions, possibly histamine-mediated, have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, bronchospasm, dyspnea, and hypotension (see section 4.8). To reduce occurrence of these reactions, do not exceed a rate of anidulafungin infusion of 1.1 mg/minute (see sections 4.2).

Risk in Patients with Hereditary Fructose Intolerance (HFI)

Anidulafungin contains fructose, an inactive ingredient, and may precipitate a metabolic crisis that may include, but is not limited to life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure in patients with HFI. Obtain careful history of HFI symptoms (nausea, vomiting, abdominal pain) with fructose/sucrose exposure prior to anidulafungin administration because a diagnosis of HFI may not yet be established in pediatric patients (see sections 4.3 and 4.6).

4.5 Drugs Interactions

Cyclosporine

Administration of multiple doses of anidulafungin and cyclosporine to healthy subjects resulted in no significant alteration in the steady state pharmacokinetics of either drug. No dosage adjustment of cyclosporine or anidulafungin is needed when the two drugs are co-administered (see section 5.3).

Voriconazole

Administration of multiple doses of anidulafungin and voriconazole to healthy subjects resulted in no significant alteration in the steady state pharmacokinetics of either drug. No dosage adjustment of voriconazole or anidulafungin is needed when the two drugs are co-administered (see section 5.3).

Tacrolimus

Administration of multiple doses of anidulafungin and a single-dose of tacrolimus to healthy subjects resulted in no significant alteration in the steady state pharmacokinetics of either drug. No dosage adjustment of tacrolimus or anidulafungin is needed when the two drugs are co-administered (see section 5.3).

Rifampicin

Administration of multiple doses of anidulafungin and rifampin to patients resulted in no significant alteration in the steady state pharmacokinetics of anidulafungin. No dosage adjustment of anidulafungin is needed when it is co-administered with rifampin (see section 5.3).

Amphotericin B Liposome for Injection

Administration of multiple doses of anidulafungin and liposomal amphotericin B to patients resulted in no significant alteration in the steady state pharmacokinetics of anidulafungin. No dosage adjustment of anidulafungin is needed when it is co-administered with liposomal amphotericin B (see section 5.3).

4.6 Use in Special Populations

Pregnancy

Risk Summary

Based on findings from animal studies, anidulafungin can cause fetal harm when administered to a pregnant woman. There are no available human data on the use of anidulafungin in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies fetal toxicity was observed in the presence of maternal toxicity when anidulafungin was administered to pregnant rabbits during organogenesis at 4 times the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area [*see Data*]. Inform pregnant woman of the risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20% respectively.

Data

Animal Data

In a combined fertility and embryo-fetal development study in rats dosed with anidulafungin for 4 weeks prior to cohabitation and through cohabitation for males or for 2 weeks prior to cohabitation and continuing through gestation day 19 for females, there was no maternal or embryo-fetal toxicity at intravenous doses up to 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).

In a rabbit embryo-fetal development study, intravenous administration of anidulafungin (0, 5, 10, and 20 mg/kg/day) from gestation day 7 through 19, resulted in reduced fetal weights and incomplete ossification in the presence of maternal toxicity (decreased body weight gain) at 20 mg/kg/day (equivalent to 4 times the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area).

In a pre- and postnatal development study, pregnant rats were intravenously administered anidulafungin at doses of 2, 6, or 20 mg/kg/day from gestation day 7 through lactation day 20. Maternal toxicity was observed at ≥ 6 mg/kg/day (clinical signs at ≥ 6 mg/kg/day and reduced body weight gain and food consumption during gestation at 20 mg/kg/day group). There were no effects on the viability or growth and development of the offspring. In this study, anidulafungin was detected in fetal plasma, indicating that it crossed the placental barrier.

Lactation

Risk Summary

There are no data on the presence of anidulafungin in human milk, the effects on the breastfed infant or the effects on milk production. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Anidulafungin was found in the milk of lactating rats [*see Data*].

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for anidulafungin and any potential adverse effects on the breastfed child from anidulafungin or from the underlying maternal condition.

Data

Animal Data

Pregnant rats were intravenously administered anidulafungin at doses of 2, 6, or 20 mg/kg/day from gestation day 7 through lactation day 20. Milk samples were collected from 5 rats per group on lactation day 14 at approximately 1 hours post dose. Approximately dose-proportional anidulafungin concentrations were found in the milk of lactating rats.

Geriatric Use

Of the total number of subjects (N = 197) in the pivotal clinical studies of anidulafungin, 35% were 65 years and over, while 18% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Dosage adjustments are not required for geriatric patients (see section 5.3).

Hepatic Insufficiency

No dosing adjustments are required for patients with any degree of hepatic insufficiency. Anidulafungin is not hepatically metabolized. Anidulafungin pharmacokinetics were examined in subjects with Child-Pugh class A, B or C hepatic insufficiency. Anidulafungin concentrations were not increased in subjects with any degree of hepatic insufficiency. Though a slight decrease in

AUC was observed in patients with Child-Pugh C hepatic insufficiency, it was within the range of population estimates noted for healthy subjects (see section 5.3).

Renal Insufficiency

Dosage adjustments are not required for patients with any degree of renal insufficiency including those on hemodialysis. Anidulafungin has negligible (<1%) renal clearance. In a clinical study of subjects with mild, moderate, severe or end stage (dialysis-dependent) renal insufficiency, anidulafungin pharmacokinetics were similar to those observed in subjects with normal renal function. Anidulafungin is not dialyzable and may be administered without regard to the timing of hemodialysis (see section 5.3).

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

The following most *serious adverse reactions* are described elsewhere in other labeling sections:

- Hepatic Adverse Reactions (see section 4.4)
- Anaphylactic and Hypersensitivity Reactions (see section 4.4)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Adults

The safety of anidulafungin for Injection was assessed in 929 individuals, including 257 healthy subjects and 672 patients in clinical trials of candidemia, other forms of *Candida* infections, and esophageal candidiasis. A total of 633 patients received anidulafungin at daily doses of either 50 mg or 100 mg. A total of 481 patients received anidulafungin for ≥14 days.

Candidemia/other Candida Infections

Three trials (one comparative vs. fluconazole, two non-comparative) assessed the efficacy and safety of anidulafungin (100 mg) in patients with candidemia and other *Candida* infections.

The data described below reflect exposure to anidulafungin and fluconazole in 127 and 118 patients, respectively, with candidemia and other forms of invasive candidiasis, in the randomized, comparative trial of the efficacy and safety of anidulafungin to that of fluconazole. In Anidulafungin-treated patients, the age range was 16-89 years, the gender distribution was 51% male and 49% female, and the race distribution was 72% White, 18% Black/African American, 9% other races. Patients were randomized to receive once daily IV anidulafungin (200 mg loading

dose followed by 100 mg maintenance dose) or IV fluconazole (800 mg loading dose followed by 400 mg maintenance dose). Treatment was administered for at least 14 and not more than 42 days.

The number of patients with adverse reactions leading to discontinuation of study medication was 11.5% in the anidulafungin arm and 21.6% in the fluconazole arm. The most common adverse reactions leading to study drug discontinuation were multi-organ failure (2.3%) and systemic *Candida* infection (1.5%) in the anidulafungin arm.

Table 2 presents adverse reactions that were reported in $\geq 5\%$ of subjects receiving anidulafungin or fluconazole therapy in this trial.

Table 2: Adverse Reactions Reported in $\geq 5\%$ of Adult Patients Receiving Anidulafungin or Fluconazole Therapy for Candidemia/other *Candida* Infections^{*,}**

Adverse Reaction	Anidulafungin 100 mg N=131	Fluconazole 400 mg N=125
	N (%)	N (%)
Subjects with a least one adverse reaction	130 (99)	122 (98)
Gastrointestinal disorders	81 (62)	72 (58)
Nausea	32 (24)	15 (12)
Diarrhea	24 (18)	23 (18)
Vomiting	23 (18)	12 (10)
Constipation	11 (8)	14 (11)
Abdominal pain	8 (6)	16 (13)
General disorders and administration site conditions	70 (53)	76 (61)
Pyrexia	23 (18)	23 (18)
Edema peripheral	14 (11)	16 (13)
Chest pain	7 (5)	6 (5)
Respiratory, thoracic, and mediastinal disorders	67 (51)	55 (44)
Dyspnea	15 (12)	4 (3)
Pleural effusion	13 (10)	11 (9)
Cough	9 (7)	7 (6)
Respiratory distress	8 (6)	2 (2)
Investigations	66 (50)	46 (37)
Blood alkaline phosphatase increased	15 (12)	14 (11)
White blood cell increased	11 (8)	3 (2)
Hepatic enzyme increased	7 (5)	14 (11)
Blood creatinine increased	7 (5)	1 (1)
Metabolism and nutrition disorders	61 (47)	61 (49)
Hypokalemia	33 (25)	24 (19)
Hypomagnesemia	15 (12)	14 (11)
Hypoglycemia	9 (7)	10 (8)
Hyperkalemia	8 (6)	14 (11)

Table 2: Adverse Reactions Reported in $\geq 5\%$ of Adult Patients Receiving Anidulafungin or Fluconazole Therapy for Candidemia/other *Candida* Infections^{*,}**

Adverse Reaction	Anidulafungin 100 mg N=131	Fluconazole 400 mg N=125
Hyperglycemia	8 (6)	8 (6)
Dehydration	8 (6)	2 (2)
Vascular disorders	50 (38)	41 (33)
Hypotension	19 (15)	18 (14)
Hypertension	15 (12)	5 (4)
Deep vein thrombosis	13 (10)	9 (7)
Psychiatric disorders	48 (37)	45 (36)
Insomnia	20 (15)	12 (10)
Confusional state	10 (8)	10 (8)
Depression	8 (6)	5 (4)
Blood and lymphatic system disorders	34 (26)	36 (29)
Anemia	12 (9)	20 (16)
Thrombocythemia	8 (6)	1 (1)
Leukocytosis	7 (5)	6 (5)
Skin and subcutaneous tissue disorders	30 (23)	32 (26)
Decubitus ulcer	7 (5)	10 (8)
Nervous system disorders	27 (21)	31 (25)
Headache	11 (8)	10 (8)
Musculoskeletal and connective tissue disorders	27 (21)	25 (20)
Back pain	7 (5)	13 (10)

* A patient who experienced multiple reactions within a Body System or preferred term was counted one time for that class, one time for the preferred term and one time for “subjects with at least one adverse reaction”.

** This trial was not designed to support comparative claims for anidulafungin for the adverse reactions reported in this table.

Esophageal Candidiasis

The data described below reflect exposure to anidulafungin and fluconazole in 300 and 301 patients, respectively, with esophageal candidiasis in a randomized trial comparing the efficacy and safety of anidulafungin to that of oral fluconazole. In Anidulafungin-treated patients, the age range was 18-68 years, the gender distribution was 42% male and 58% female and the race distribution was 15% White, 49% Black/African American, 15% Asian, 0.3% Hispanic, 21% other races. Patients were randomized to receive IV anidulafungin (100 mg on day 1, followed by 50 mg per day) or oral fluconazole (200 mg on day 1, followed by 100 mg per day) for 7 days beyond resolution of symptoms (range, 14-21 days).

Twenty-eight (9%) patients in the anidulafungin arm and 36 (12%) patients in the fluconazole arm had adverse reactions related to study medication. The most common adverse reactions leading to study discontinuation were maculopapular rash (1 patient) for the anidulafungin arm. The most common adverse reactions leading to discontinuation were rash (1 patient) and increased AST (1 patient) for the fluconazole arm.

Table 3 presents adverse reactions that were reported in $\geq 5\%$ of subjects receiving anidulafungin therapy.

Table 3: Adverse Reactions Reported in $\geq 5\%$ of Adult Patients Receiving Anidulafungin or Fluconazole Therapy for Esophageal Candidiasis^{*,}**

Adverse Reaction	Anidulafungin 50 mg N=300	Fluconazole 100 mg N=301
	N (%)	N (%)
Subjects with a least one adverse reaction	239 (80)	227 (75)
Infections and infestations	115 (38)	99 (33)
Oral candidiasis	15 (5)	10 (3)
Gastrointestinal disorders	106 (35)	113 (38)
Diarrhea	27 (9)	26 (9)
Vomiting	27 (7)	30 (10)
Nausea	20 (7)	23 (8)
Dyspepsia	20 (7)	21 (7)
Blood and lymphatic system disorders	55 (18)	50 (17)
Anemia	25 (8)	22 (7)
Metabolism and nutrition disorders	50 (17)	46 (15)
Hypokalemia	14 (5)	17 (6)
General disorders and administration site condition	49 (16)	54 (18)
Pyrexia	27 (9)	28 (9)
Nervous system disorders	39 (13)	36 (12)
Headache	25 (8)	20 (7)

* A patient who experienced multiple reactions within a Body System or preferred term was counted one time for that class, one time for the preferred term and one time for “subjects with at least one adverse reaction”.

** This trial was not designed to support comparative claims for anidulafungin for the adverse reactions reported in this table.

Less Common Adverse Reactions in Adult Patients with Candidemia/other Candida Infections and Esophageal Candidiasis

The following selected adverse reactions occurred in $<2\%$ of patients:

Blood and Lymphatic: coagulopathy, thrombocytopenia

Cardiac: atrial fibrillation, bundle branch block (right), sinus arrhythmia, ventricular extrasystoles

Eye: eye pain, vision blurred, visual disturbance

General and Administration Site: infusion related reaction, peripheral edema, rigors

Hepatobiliary: abnormal liver function tests, cholestasis, hepatic necrosis

Infections: clostridial infection

Investigations: amylase increased, bilirubin increased, CPK increased, electrocardiogram QT prolonged, gamma-glutamyl transferase increased, lipase increased, potassium decreased, prothrombin time prolonged, urea increased

Nervous System: convulsion, dizziness

Respiratory, Thoracic and Mediastinal: cough

Skin and Subcutaneous Tissue: angioneurotic edema, erythema, pruritus, sweating increased, urticaria

Vascular: flushing, hot flushes, thrombophlebitis superficial

Clinical Trials Experience in Pediatric Patients with Candidemia/Invasive Candidiasis

The safety of anidulafungin was investigated in 68 pediatric patients from 1 month to less than 18 years of age with candidemia/invasive candidiasis in a prospective, open-label, non-comparative pediatric trial (see section 5.2, Clinical studies). Overall, the safety profile of anidulafungin in the pediatric patients 1 month and older was similar to that of adults.

Most Common Adverse Reactions

The most common adverse reactions occurring in $\geq 5\%$ of pediatric patients receiving anidulafungin therapy in the clinical trial are displayed by body system in Table 4.

Table 4 Adverse Reactions Occurring in $\geq 5\%$ of Pediatric Patients Receiving Anidulafungin Therapy for Candidemia/other *Candida* Infections*,**

Adverse Reaction	1 month to <2 years N=19	2 to <5 years N=19	5 to <18 years N=30	Overall N=68
	n (%)	n (%)	n (%)	n (%)
Subjects with a least one adverse reaction	17 (90)	14 (74)	24 (80)	55 (81)
Blood and lymphatic system disorders	9 (47)	3 (16)	4 (13)	16 (24)
Anemia	5 (26)	2 (11)	0	7 (10)
Thrombocytopenia	2 (11)	1 (5)	1 (3)	4 (6)
Gastrointestinal disorders	8 (42)	8 (42)	12 (40)	28 (41)
Diarrhea	4 (21)	2 (11)	5 (17)	11 (16)
Vomiting	4 (21)	5 (26)	2 (7)	11 (16)
Abdominal pain ^a	0	4 (21)	2 (7)	6 (9)
General disorders and administration site condition	5 (26)	6 (32)	9 (30)	20 (29)
Pyrexia	4 (21)	3 (16)	5 (17)	12 (18)
Laboratory investigations	4 (21)	4 (21)	8 (27)	16 (24)
Alanine aminotransferase increased	2 (11)	2 (11)	2 (7)	6 (9)
Aspartate aminotransferase increased	2 (11)	1 (5)	1 (3)	4 (6)
Metabolism and nutrition disorders	3 (16)	4 (21)	6 (20)	13 (19)
Hypoglycemia	1 (5)	2 (11)	1 (3)	4 (6)
Respiratory, thoracic and mediastinal disorders	5 (26)	5 (26)	5 (17)	15 (22)
Epistaxis	1 (5)	2 (11)	3 (10)	6 (9)

Table 4 Adverse Reactions Occurring in $\geq 5\%$ of Pediatric Patients Receiving Anidulafungin Therapy for Candidemia/other *Candida* Infections*,**

Adverse Reaction	1 month to <2 years N=19	2 to <5 years N=19	5 to <18 years N=30	Overall N=68
Skin and subcutaneous tissue disorders	6 (32)	5 (26)	5 (17)	16 (24)
Rash ^b	3 (16)	1 (5)	2 (7)	6 (9)

* Reflects adverse reactions including those that started on or after first dose of anidulafungin through 6-week follow-up for patients who did not receive oral fluconazole, and those that started between first dose and last dose of anidulafungin for patients who received oral fluconazole.

** A patient who experienced multiple reactions within a Body System or preferred term was counted one time for that class, one time for the preferred term and one time for “subjects with at least one adverse reaction”.

^a Includes such terms as: abdominal pain and abdominal pain upper.

^b Includes such terms as: rash and rash generalized.

Other adverse reactions were reported in 2 or more pediatric patients and in less than 5% of the 68 pediatric patients treated with anidulafungin in the clinical trial:

Blood and Lymphatic System Disorders: pancytopenia, thrombocytosis, febrile neutropenia, leukopenia, neutropenia

Eye Disorders: Periorbital edema

Gastrointestinal Disorders: gastroesophageal reflux disease, abdominal distension, nausea, stomatitis, dry mouth

General Disorders and Administrative Site Conditions: chest pain, edema peripheral

Infections and Infestations: bacteremia, device related infection, gastroenteritis, lower respiratory tract infection, upper respiratory tract infection, urinary tract infection

Laboratory Investigations: gamma-glutamyltransferase increased, transaminases increased

Metabolism and Nutrition Disorders: hypocalcemia, hypokalemia, hyponatremia, hypoproteinemia

Musculoskeletal and Connective Tissue Disorders: back pain, pain in extremity

Nervous System Disorders: headache, tremor, seizure

Psychiatric Disorders: agitation

Respiratory, Thoracic and Mediastinal Disorders: hemoptysis

Vascular Disorders: hypotension

Post-marketing Experience

The following adverse reactions have been identified during post approval use of anidulafungin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune: Anaphylactic shock, anaphylactic reaction, bronchospasm (see section 4.4).

4.9 Overdose

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, 3 of the 10 subjects experienced transient, asymptomatic transaminase elevations ($\leq 3 \times \text{ULN}$) (see section 4.4).

Anidulafungin is not dialyzable.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of Action

Anidulafungin is an anti-fungal drug.

Anidulafungin is a semi-synthetic echinocandin with antifungal activity. Anidulafungin inhibits glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3- β -D-glucan, an essential component of the fungal cell wall.

5.2. Pharmacodynamic Properties

Resistance

Echinocandin resistance is due to point mutations within the genes (FKS1 and FKS2) encoding for subunits in the glucan synthase enzyme complex. There have been reports of *Candida* isolates with reduced susceptibility to anidulafungin, suggesting a potential for development of drug resistance. The clinical significance of this observation is not fully understood.

Antimicrobial Activity

Anidulafungin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections:

Candida albicans

Candida glabrata

Candida parapsilosis

Candida tropicalis.

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following fungi exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for anidulafungin against isolates of the following *Candida* species. However, the effectiveness of anidulafungin in treating clinical infections due to these fungi has not been established in adequate and well-controlled clinical trials:

Candida guilliermondii
Candida krusei

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug.

Clinical Studies

Candidemia and other *Candida* Infections (Intra-abdominal Abscess and Peritonitis)

Adults Candidemia and Other *Candida* Infections (Intra-abdominal Abscess and Peritonitis) Trial

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

Patients who received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site before entry into the study (modified intent-to-treat [MITT] population) were included in the analysis of global response at the end of IV therapy. A successful global response required clinical cure or improvement (significant, but incomplete resolution of signs and symptoms of the *Candida* infection and no additional antifungal treatment), and documented or presumed microbiological eradication. Patients with an indeterminate outcome were analyzed as failures in this population.

Two hundred and fifty-six patients in the intent-to-treat (ITT) population were randomized and received at least one dose of study medication.

In Anidulafungin-treated patients, the age range was 16-89 years, the gender distribution was 50% male and 50% female, and the race distribution was 71% White, 20% Black/African American, 7% Hispanic, 2% other races. The median duration of IV therapy was 14 and 11 days in the anidulafungin and fluconazole arms, respectively. For those who received oral fluconazole, the median duration of oral therapy was 7 days for the anidulafungin arm and 5 days for the fluconazole arm.

Patient disposition is presented in Table 5.

Table 5: Patient Disposition and Reasons for Discontinuation in Candidemia and other *Candida* Infections Study

	Anidulafungin	Fluconazole
	n (%)	n (%)
Treated patients	131	125
Patients completing study through 6 week follow-up	94 (72)	80 (64)
DISCONTINUATIONS FROM STUDY MEDICATION		
Total discontinued from study medication	34 (26)	48 (38)
Discontinued due to adverse events	12 (9)	21 (17)
Discontinued due to lack of efficacy	11 (8)	16 (13)

Two hundred and forty-five patients (127 anidulafungin, 118 fluconazole) met the criteria for inclusion in the MITT population. Of these, 219 patients (116 anidulafungin, 103 fluconazole) had candidemia only. Risk factors for candidemia among patients in both treatment arms in this study were: presence of a central venous catheter (78%), receipt of broad-spectrum antibiotics (69%), recent surgery (42%), recent hyperalimentation (25%), and underlying malignancy (22%). The most frequent species isolated at baseline was *C. albicans* (62%), followed by *C. glabrata* (20%), *C. parapsilosis* (12%) and *C. tropicalis* (11%). The majority (97%) of patients were non-neutropenic (ANC >500) and 81% had APACHE II scores less than or equal to 20.

Global success rates in patients with candidemia and other *Candida* infections are summarized in Table 6.

Table 6: Efficacy Analysis: Global Success in patients with Candidemia and other *Candida* Infections (MITT Population)

Time-point	Anidulafungin (N=127) n (%)	Fluconazole (N=118) n (%)	Treatment Difference^a, % (95% C.I.)
End of IV Therapy	96 (75.6)	71 (60.2)	15.4 (3.9, 27.0)
End of All Therapy ^b	94 (74.0)	67 (56.8)	17.2 (2.9, 31.6) ^c
2 Week Follow-up	82 (64.6)	58 (49.2)	15.4 (0.4, 30.4) ^c
6 Week Follow-up	71 (55.9)	52 (44.1)	11.8 (-3.4, 27.0) ^c

^a Calculated as anidulafungin minus fluconazole

^b 33 patients in each study arm (26% anidulafungin and 29% fluconazole-treated) switched to oral fluconazole after the end of IV therapy.

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

Table 7 presents global response by patients with candidemia or multiple sites of *Candida* infection and mortality data for the MITT population.

Table 7: Global Response and Mortality in Candidemia and other *Candida* Infections

	Anidulafungin	Fluconazole	Between group difference^a (95% CI)
No. of MITT patients	127	118	
Global Success (MITT) At End of IV Therapy			
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 <i>Candida</i>	2/127 (1.6%)	5/118 (4.2%)	-

^a Calculated as anidulafungin minus fluconazole

Pediatric Candidemia/Invasive Candidiasis Trial

A prospective, open-label, non-comparative, multinational trial (National Clinical Trial (NCT) number 00761267) assessed the safety and efficacy of anidulafungin in 68 pediatric patients aged 1 month to <18 years with candidemia/invasive candidiasis. 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 mg/kg loading dose on Day 1, and 1.5 mg/kg daily maintenance dose thereafter) followed by an optional switch to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) up to Day 49. Patients were followed at 2 and 6 weeks after EOT.

Among 68 Anidulafungin-treated patients, 64 had microbiologically confirmed *Candida* infection and were evaluated for efficacy in the modified intent-to-treat (MITT) population. Overall, 59 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 successful clinical (cure or improvement) and microbiological (eradication or

presumed eradication) response. The overall rates of successful global response in the MITT population are presented in Table 8 below.

Table 8: Summary of Successful Global Response by Age Group, MITT Population

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

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

Esophageal Candidiasis

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

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

Treatment groups were similar in demographic and other baseline characteristics. In Anidulafungin-treated patients, the age range was 16-69 years, the gender distribution was 42% male and 58% female, and the race distribution was 15% White, 49% Black/African American, 15% Asian, 0.3 % Hispanic, 21% other races.

In this study, of 280 patients tested, 237 (84.6%) tested HIV positive. In both groups the median time to resolution of symptoms was 5 days and the median duration of therapy was 14 days.

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

An endoscopic success, defined as cure (endoscopic grade of 0 on a 4 point severity scale) or improvement (decrease of one or more grades from baseline), was seen in 225/231 (97.4%) anidulafungin-treated patients and 233/236 (98.7%) fluconazole-treated patients (Table 9). The majority of these patients were endoscopic cures (grade=0). Two weeks after completing therapy,

the anidulafungin group had significantly more endoscopically-documented relapses than the fluconazole group, 120/225 (53.3%) vs. 45/233 (19.3%), respectively (Table 9).

Table 9: Endoscopy Results in Patients with Esophageal Candidiasis (Clinically Evaluable Population)

Endoscopic Response at End of Therapy				
Response	Anidulafungin N=231	Fluconazole N=236	Treatment Difference ^a	95% CI
Endoscopic Success, n (%)	225 (97.4)	233 (98.7)	-1.3%	-3.8%, 1.2%
Cure	204 (88.3)	221 (93.6)		
Improvement	21 (9.1)	12 (5.1)		
Failure, n (%)	6 (2.6)	3 (1.3)		
Endoscopic Relapse Rates at Follow-Up, 2 Weeks Post-Treatment				
	Anidulafungin	Fluconazole	Treatment Difference ^a	95% CI
Endoscopic Relapse, n/N (%)	120/225 (53.3%)	45/233 (19.3%)	34.0%	25.8%, 42.3%

^a Calculated as anidulafungin minus fluconazole

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

5.3. Pharmacokinetic Properties

General Pharmacokinetic Characteristics

The pharmacokinetics of anidulafungin following intravenous (IV) administration of anidulafungin have been characterized in healthy subjects, special populations and patients. Systemic exposures of anidulafungin are dose-proportional and have low inter-subject variability (coefficient of variation <25%) as shown in Table 10. The steady state was achieved on the first day after a loading dose (twice the daily maintenance dose) and the estimated plasma accumulation factor at steady state is approximately 2.

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

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

^a Parameters were obtained from separate studies.

^b LD/MD: loading dose/maintenance dose once daily.

^c Data were collected on Day 7

^d Safety and efficacy of these doses has not been established.

^e See OVERDOSAGE.

C_{max, ss} = the steady state peak concentration

AUC_{ss} = the steady state area under concentration vs. time curve

CL = clearance

t_{1/2} = the terminal elimination half-life

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

Distribution

The pharmacokinetics of anidulafungin following IV administration are characterized by a short distribution half-life (0.5-1 hour) and a volume of distribution of 30-50 L that is similar to total body fluid volume. Anidulafungin is 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 (CYP450) isoenzymes. It is unlikely that anidulafungin will have clinically relevant effects on the metabolism of drugs metabolized by CYP450 isoenzymes.

Anidulafungin undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide that lacks antifungal activity. The *in vitro* degradation half-life of anidulafungin under physiologic conditions is about 24 hours. *In vivo*, the ring-opened product is subsequently converted to peptidic degradants and eliminated.

Excretion

In a single-dose clinical study, radiolabeled (¹⁴C) anidulafungin was administered to healthy subjects. Approximately 30% of the administered radioactive dose was eliminated in the feces over 9 days, of which less than 10% was intact drug. Less than 1% of the administered radioactive dose was excreted in the urine. Anidulafungin concentrations fell below the lower limits of quantitation 6 days post-dose. Negligible amounts of drug-derived radioactivity were recovered in blood, urine, and feces 8 weeks post-dose.

Specific Populations

Patients with fungal infections

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

The pharmacokinetics of anidulafungin in patients with fungal infections are similar to those observed in healthy subjects. The pharmacokinetic parameters of anidulafungin estimated using population pharmacokinetic modeling following IV administration of a maintenance dose of 50 mg/day or 100 mg/day (following a loading dose) of anidulafungin are presented in Table 11.

Table 11: 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, β} [h] ^b	26.5 (28.5)	

^a All the parameters were estimated by population modeling using a two-compartment model with first order elimination; 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 and 100 mg/day.

^b t_{1/2, β} is the predominant elimination half-life that characterizes the majority of the concentration-time profile.

^c LD/MD: loading dose/daily maintenance dose.

Gender

Dosage adjustments are not required based on gender. Plasma concentrations of anidulafungin in healthy men and women were similar. In multiple-dose patient studies, drug clearance was slightly faster (approximately 22%) in men.

Geriatric

Dosage adjustments are not required for geriatric patients. The population pharmacokinetic analysis showed that median clearance differed slightly between the elderly group (patients ≥65, median CL = 1.07 L/h) and the non-elderly group (patients <65, median CL = 1.22 L/h) and the range of clearance was similar.

Race

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

HIV Status

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

Hepatic Insufficiency

Anidulafungin is not hepatically metabolized. Anidulafungin pharmacokinetics were examined in subjects with Child-Pugh class A, B or C hepatic insufficiency. Anidulafungin concentrations were not increased in subjects with any degree of hepatic insufficiency. Though a slight decrease in AUC was observed in patients with Child-Pugh C hepatic insufficiency, it was within the range of population estimates noted for healthy subjects (see section 4.6).

Renal Insufficiency

Anidulafungin has negligible renal clearance. In a clinical study of subjects with mild, moderate, severe or end stage (dialysis-dependent) renal insufficiency, anidulafungin pharmacokinetics were similar to those observed in subjects with normal renal function. Anidulafungin is not dialyzable and may be administered without regard to the timing of hemodialysis (see section 4.6).

Pediatric

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

Table 12: Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin Once Daily in Pediatric Patients

PK Parameter ^a	Anidulafungin IV Dosing Regimen (LD/MD, mg/kg) ^b			
	1.5/0.75		3.0/1.5	
Age Group	2-11 years (N = 6)	12-17 years (N = 6)	2-11 years (N = 6)	12-17 years (N = 6)
$C_{max, ss}$ [mg/L]	3.32 (50.0)	4.35 (22.5)	7.57 (34.2)	6.88 (24.3)
AUC_{ss} [mg·h/L]	41.1 (38.4)	56.2 (27.8)	96.1 (39.5)	102.9 (28.2)

^a Data were collected on Day 5

^b LD/MD: loading dose/daily maintenance dose

The pharmacokinetics of anidulafungin were also investigated in 66 pediatric patients (1 month to <18 years) with candidemia/invasive candidiasis (ICC) in a prospective, open-label, non-comparative pediatric study following administration of anidulafungin of 3 mg/kg loading dose on Day 1 and followed by 1.5 mg/kg once daily maintenance dose (see section 5.2, Clinical Studies). Based on population pharmacokinetic analysis of combined data from adult and pediatric patients with ICC, the mean steady state exposure parameters ($AUC_{0-24,ss}$, $C_{min,ss}$ and $C_{max,ss}$) across age groups in the overall pediatric patients (Table 13) were comparable to those in adults receiving 200 mg loading dose and 100 mg once daily maintenance dose.

Table 13: Mean (%CV) Steady State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin in Pediatric Patients with Candidemia/Invasive Candidiasis Estimated Using Population Pharmacokinetic Modeling

PK Parameter	Anidulafungin IV Dosing Regimen (3 mg/kg LD/1.5 mg/kg MD) ^a		
	1 month to <2 years (N = 17)	2 to < 5 years (N = 19)	5 to <18 years (N = 30)
C _{max, ss} [mg/L]	6.7 (28.3)	7.1 (39.4)	6.5 (29.2)
C _{min, ss} [mg/L]	2.0 (29)	2.5 (44)	2.5 (38.4)
AUC _{ss} [mg·h/L]	69.9 (25.3)	82.8 (38.5)	86.8 (35.8)

^a LD/MD: loading dose on Day 1/ once daily maintenance dose.

Drug Interactions

In vitro studies showed that anidulafungin is not metabolized by human cytochrome P450 or by isolated human hepatocytes and does not significantly inhibit the activities of human CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A) in clinically relevant concentrations. No clinically relevant drug-drug interactions were observed with drugs likely to be co-administered with anidulafungin.

Cyclosporine (CYP3A4 substrate)

In a study in which 12 healthy adult subjects received 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose (on Days 1 to 8) and in combination with 1.25 mg/kg oral cyclosporine twice daily (on Days 5 to 8), the steady state C_{max} of anidulafungin was not significantly altered by cyclosporine; the steady state AUC of anidulafungin was increased by 22%. A separate *in vitro* study showed that anidulafungin has no effect on the metabolism of cyclosporine (see section 4.5).

Voriconazole (CYP2C19, CYP2C9, CYP3A4 inhibitor and substrate)

In a study in which 17 healthy subjects received 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose, 200 mg twice daily oral voriconazole (following two 400 mg loading doses) and both in combination, the steady state C_{max} and AUC of anidulafungin and voriconazole were not significantly altered by co-administration (see section 4.5).

Tacrolimus (CYP3A4 substrate)

In a study in which 35 healthy subjects received a single oral dose of 5 mg tacrolimus (on Day 1), 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose (on Days 4 to 12) and both in combination (on Day 13), the steady state C_{max} and AUC of anidulafungin and tacrolimus were not significantly altered by co-administration (see section 4.5).

Rifampin (potent CYP450 inducer)

The pharmacokinetics of anidulafungin were examined in 27 patients that were co-administered anidulafungin and rifampin. The population pharmacokinetic analysis showed that when compared

to data from patients that did not receive rifampin, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with rifampin (see section 4.5).

Amphotericin B liposome for injection

The pharmacokinetics of anidulafungin were examined in 27 patients that were co-administered liposomal amphotericin B. The population pharmacokinetic analysis showed that when compared to data from patients that did not receive amphotericin B, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with amphotericin B (see section 4.5).

Microbiology

Mechanism of Action

Anidulafungin is a semi-synthetic echinocandin with antifungal activity. Anidulafungin inhibits glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3- β -D-glucan, an essential component of the fungal cell wall.

Resistance

Echinocandin resistance is due to point mutations within the genes (*FKS1* and *FKS2*) encoding for subunits in the glucan synthase enzyme complex. There have been reports of *Candida* isolates with reduced susceptibility to anidulafungin, suggesting a potential for development of drug resistance. The clinical significance of this observation is not fully understood.

Antimicrobial Activity

Anidulafungin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections:

Candida albicans

Candida glabrata

Candida parapsilosis

Candida tropicalis

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following fungi exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for anidulafungin against isolates of the following *Candida* species. However, the effectiveness of anidulafungin in treating clinical infections due to these fungi has not been established in adequate and well-controlled clinical trials:

Candida guilliermondii

Candida krusei

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

6. NONCLINICAL PARTICULARS

6.1 Animal Toxicology or Pharmacology

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

7. DESCRIPTION

White to off-white lyophilized solid.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

This medicinal product must not be mixed or coadministered with other medicinal products or electrolytes except those mentioned in section 8.4.

8.2 Shelf-life

3 years

8.3 Packaging Information

100 mg lyophile in a 30 mL Type 1 glass vial with an elastomeric stopper (butyl rubber with an inert polymer coating on the product contact surface and lubricant on the top surface for easier machinability) and aluminum seal with flip-off cap.

Anidulafungin will be marketed as a box containing:

1 vial of 100 mg powder

8.4 Storage and Handling Instructions

Anidulafungin vials

Anidulafungin (unreconstituted) vials should be stored in a refrigerator 2°C - 8°C (36°F – 46°F). Do not freeze.

Excursions for 96 hours up to 25°C (77°F) are permitted, and the vial can be returned to storage at 2°C – 8°C (36°F – 46°F).

Reconstituted Solution:

Anidulafungin reconstituted solution can be stored at up to 25°C (77°F) for up to 24 hours (see section 4.2).

Infusion Solution:

Anidulafungin infusion solution can be stored at temperatures up to 25°C (77°F) for up to 48 hours. Do not freeze (see section 4.2).

9. PATIENT COUNSELLING INFORMATION

Hepatic Adverse Reactions

Inform patients about the risk of developing abnormal liver function tests and/or hepatic dysfunction. Advise the patient that liver function tests may be monitored during treatment.

Anaphylactic and Hypersensitivity Reactions

Inform the patient that anaphylactic reactions, including shock were reported with anidulafungin. Inform the patient if these reactions occur, anidulafungin may be discontinued and appropriate treatment administered.

Inform the patient that anidulafungin is also known to cause infusion-related adverse reactions, possibly histamine-mediated. Inform the patient to report symptoms including rash, urticaria, flushing, pruritus, dyspnea, and hypotension to their healthcare provider.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk of anidulafungin to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Patients with Hereditary Fructose Intolerance (HFI)

Inform patients and caregivers that anidulafungin contains fructose and can be life-threatening when administered to patients with hereditary fructose intolerance (HFI) (see section 4.4). Inquire for symptoms of fructose and/or sucrose intolerance.

10. DETAILS OF MANUFACTURER

M/s Pharmacia & Upjohn Company LLC, 7000 Portage Road, Kalamazoo-49001, Michigan, USA

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Import-87/09 dated 26 February 2009

12. DATE OF REVISION

March 2021