ANIDULAFUNGIN

ERAXIS™

℞

100 mg Lyophilized Powder for Injection (IV Infusion)

1. PHARMACOLOGIC CATEGORY

Antimycotic

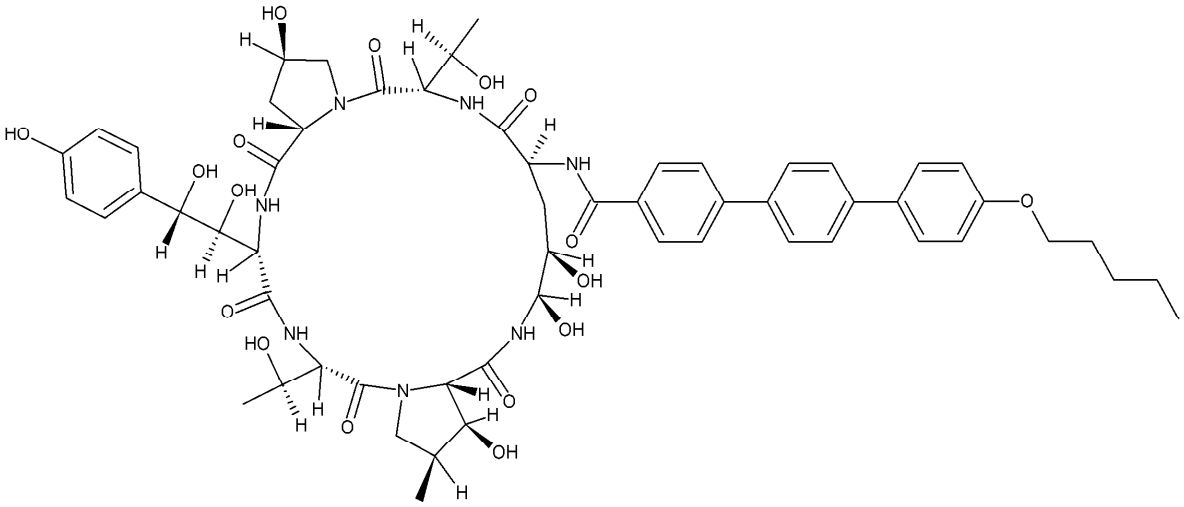
2. DESCRIPTION

Anidulafungin (Eraxis™) is a semi-synthetic echinocandin, a lipopeptide synthesized from a fermentation product of *Aspergillus nidulans.* Anidulafungin selectively inhibits 1,3-ß-D-glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3-ß-D-glucan, an essential component of the fungal cell wall. It has shown fungicidal activity against *Candida* species and activity against regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

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

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

The structural formula is:



3. FORMULATION/COMPOSITION

Vials containing 100 mg anidulafungin powder and solvent for solution for infusion (see section **6.4 Availability**).

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

For a full list of excipients, see section **6.1 List of Excipients**.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Treatment of invasive candidiasis, including candidemia, in adult and in pediatric patients one month and older (see section **5.1 Pharmacodynamic Properties**).

Treatment of esophageal candidiasis, in adult patients (see section **5.1 Pharmacodynamic Properties**).

4.2. Dosage and Method of Administration

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

Adult patients

For patients with hereditary fructose intolerance (HFI) see section **4.4 Special Warnings and Precautions for Use**.

Invasive candidiasis, including candidemia
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.

Esophageal candidiasis

The recommended dose is a single 100 mg loading dose of anidulafungin on Day 1, followed by 50 mg daily thereafter. Patients should be treated for a minimum of 14 days and for at least 7 days following resolution of symptoms. Duration of treatment should be based on the patient's clinical response. Because of the risk of relapse of esophageal

candidiasis in patients with HIV infections, suppressive antifungal therapy may be considered after a course of treatment.

Pediatric patients (one month and older)

For patients with HFI and all patients under 2 years of age, see section **4.4 Special Warnings and Precautions for Use**.

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 **4.4 Special Warnings and Precautions for Use**).

Anidulafungin 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 **6.6 Special Precautions for Disposal and Other Handling**.

It is recommended that anidulafungin is administered at a maximum rate of infusion that does not exceed 1.1 mg/minute (see sections **4.4 Special Warnings and Precautions for Use, 4.8 Undesirable Effects** and **6.6 Special Precautions for Disposal and Other Handling**).

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 section **5.2 Pharmacokinetic Properties**).

Other special populations
No dosing adjustments are required for adult patients based on patient gender, weight, ethnicity, HIV positivity, or geriatric status.

4.3. Contraindications

Hypersensitivity to the active substance, or to any of the excipients.

Hypersensitivity to other medicinal products of the echinocandin class (e.g. caspofungin).

4.4. Special Warnings and Precautions for Use

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

Infusion-related reactions
Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, bronchospasm and hypotension. Infusion-related adverse events are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute. (see sections **4.2 Dosage and Method of Administration**, **4.8 Undesirable Effects** and **6.6 Special Precautions for Disposal and Other Handling**)

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

Patients with hereditary fructose intolerance
Patients with hereditary fructose intolerance (HFI) should not be given this medicine unless strictly necessary.

A detailed history with regard to HFI symptoms should be taken of each patient prior to being given this medicinal product.

Infants and children below 2 years of age may not yet be diagnosed with HFI. Medicines containing fructose given intravenously may be life-threatening and should not be administered in this population unless there is an overwhelming clinical need and no alternatives are available.

Pediatric population
Treatment with anidulafungin in neonates (less than 1 month old) is not recommended. Treating neonates requires consideration for coverage of disseminated candidiasis including Central Nervous System (CNS); nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate CNS penetration (see section **5.3 Preclinical Safety Data**), 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.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

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 the concomitant medications (see section **5.2 Pharmacokinetic Properties**).

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, 3A) at clinically relevant concentrations.

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

Cyclosporin (CYP3A4 substrate): In a study of 12 healthy adult subjects who received 100 mg/day anidulafungin following a 200 mg loading dose alone and in combination with 1.25 mg/kg oral cyclosporin twice daily, the steady state plasma peak concentration (C_{max}) of anidulafungin was not significantly altered by cyclosporin; however the steady state area under the concentration-time curve (AUC) was increased by 22%. An *in vitro* study has shown that anidulafungin has no effect on the metabolism of cyclosporin. Adverse events observed in this study were consistent with those observed in other studies where anidulafungin only was administered. No dosage adjustment of either drug is required when they are co-administered.

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

Tacrolimus (CYP3A4 substrate): In a study of 35 healthy subjects who received a single oral dose of 5 mg tacrolimus alone, 100 mg/day anidulafungin alone following a 200 mg loading dose and both in combination, the steady-state C_{max} and AUC of anidulafungin and tacrolimus were not significantly altered by co-administration. No dosage adjustment of either drug is required when co-administered.

***Liposomal amphotericin B*:** The pharmacokinetics of anidulafungin were examined in 27 patients (100 mg/day anidulafungin) who were co-administered with liposomal amphotericin B (doses up to 5 mg/kg/day). The population pharmacokinetic analysis showed that, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with amphotericin B when compared to data from patients who did not receive amphotericin B. No dosage adjustment of anidulafungin is required.

Rifampicin (potent CYP450 inducer): The pharmacokinetics of anidulafungin were examined in 27 patients (50 or 75 mg/day anidulafungin) who were co-administered with rifampicin (doses up to 600 mg/day). The population pharmacokinetic analysis showed that when compared to data from patients that did not receive rifampicin, the pharmacokinetics of anidulafungin were not significantly altered by co-administration with rifampicin. No dosage adjustment of anidulafungin is required.

4.6. Fertility, Pregnancy and Lactation

Animal studies have shown no selective reproductive toxicity (see section **5.3 Preclinical Safety Data**). There are no adequate or well-controlled data regarding the use of anidulafungin in pregnant women. Therefore, anidulafungin should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the fetus.

Animal studies have shown excretion of anidulafungin in breast milk. 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 mother.

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

Fifteen hundred and sixty-five (1565) patients received intravenous anidulafungin in clinical trials (1308 in Phase 2/3 studies and 257 in Phase I studies).

The safety profile of anidulafungin is based on 840 patients with candidemia/invasive candidiasis receiving the recommended daily dose of 100 mg in 9 studies. Three studies (one comparative vs. fluconazole, 2 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/candidemia (ICC) database] a total of 204 patients received anidulafungin, 119 for ≥14 days. In six additional studies (two comparative vs. caspofungin and four non-comparative), 636 patients including 53 neutropenic patients and 131 patients with deep tissue infection were studied; the mean durations of intravenous treatment in neutropenic patients and patients with deep tissue infection in these studies were 10.0 (range, 1 to 42 days) and 14.0 (range, 1 to 42 days) days, respectively. Adverse events were typically mild to moderate and seldom led to discontinuation.

The following table includes the all-causality adverse events (MedDRA terms) from 840 subjects receiving 100 mg anidulafungin.

Infusion-related adverse events have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, bronchospasm and hypotension (see section **4.4 Special Warnings and Precautions for Use**).

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Infections and infestations	Clostridium colitis Fungemia Candidiasis Oral candidiasis
Blood and lymphatic system disorders	Thrombocytopenia Thrombocythemia Coagulopathy
Immune system disorders	Anaphylactic shock*,# Anaphylactic reaction*,#
Metabolism and nutrition disorders	Hypokalemia Hyperkalemia Hyperglycemia Hypomagnesemia Hypercalcemia Hypernatremia
Nervous system disorders	Convulsion Headache
Eye disorders	Vision blurred Visual disturbance Eye pain
Cardiac disorders	Atrial fibrillation Ventricular extrasystoles Sinus arrhythmia Bundle branch block right
Vascular disorders	Thrombosis Hypertension Flushing Hot flush
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Fecal incontinence Diarrhea Nausea Vomiting Constipation Abdominal pain upper
Hepatobiliary disorders	Cholestasis
Skin and subcutaneous tissue disorders	Urticaria Pruritus generalized Rash Pruritus
Musculoskeletal and connective tissue disorders	Back pain

General disorders and administration site conditions	Infusion site pain
Investigations	Electrocardiogram QT prolonged Electrocardiogram abnormal Blood potassium decreased Platelet count decreased Blood creatinine increased Blood urea increased Blood amylase increased Lipase increased Alanine aminotransferase increased Blood alkaline phosphatase increased Aspartate aminotransferase increased Blood bilirubin increased Liver function test abnormal Blood magnesium decreased Gamma-glutamyltransferase increased Hepatic enzyme increased Transaminases increased Platelet count increased

***** ADR identified post-marketing.
[#] See section **4.4 Special Warnings and Precautions for Use**.

In the safety assessment of the Phase 2/3 patient population (N = 669), the following additional adverse events were of note: neutropenia, leukopenia, anemia, hyperuricemia, hypocalcemia, hyponatremia, hypoalbuminemia, hypophosphatemia, anxiety, delirium, confusional state, hallucination auditory, dizziness, paresthesia, central pontine myelinolysis, dysgeusia, Guillain-Barré syndrome, tremor, altered visual depth perception, deafness unilateral, phlebitis, thrombophlebitis superficial, hypotension, lymphangitis, dyspepsia, dry mouth, esophageal ulcer, hepatic necrosis, angioneurotic edema, hyperhidrosis, myalgia, monoarthritis, renal failure, hematuria, pyrexia, chills, edema peripheral, injection site reaction, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, lymphocyte count decreased.

Pediatric population

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 pediatric study (see section **5.1 Pharmacodynamic Properties**). The adverse event profile of these 68 pediatric subjects was similar to that observed in adults with ICC but hepatobiliary adverse events, in particular Alanine aminotransferase (ALT) increased and Aspartate aminotransferase (AST) increased appeared at a higher frequency in these pediatric patients than has been observed in adults. 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.

4.9. Overdose and Treatment

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 dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

General Properties

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics
ATC code: JO2 AX 06

Mode of Action
Anidulafungin is a semi-synthetic echinocandin, a lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*.

Anidulafungin selectively inhibits 1,3-β-D glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. Anidulafungin has shown fungicidal activity against *Candida* species and activity against regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

Activity in vitro
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.

MICs were determined according to the Clinical and Laboratory Standard Institute (CLSI) approved standard reference methods M27 and M38. 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.

In combination with other antifungal agents
In vitro studies of anidulafungin in combination with fluconazole, itraconazole and amphotericin B suggest no antagonism of antifungal activity against *Candida* species. The clinical significance of these results is unknown. *In vitro* studies have evaluated the activity of anidulafungin in combination with itraconazole, voriconazole, and amphotericin B against *Aspergillus* spp. The combination of anidulafungin and amphotericin B showed indifference for 16 of 26 isolates, while anidulafungin in combination with either itraconazole or voriconazole showed synergy against 18 of 26 isolates. The clinical significance of these results is unknown.

Information from Clinical Studies

Candidemia and Other Forms of Invasive Candidiasis
The safety and efficacy of anidulafungin were evaluated in a pivotal, Phase 3, randomized, double-blind, multicenter, multinational study of patients with candidemia. 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 six weeks beyond the end of all therapy.

Two hundred and fifty-six patients (aged 16 to 91 years) were randomized to treatment and received at least one dose of study medication. 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 (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.

At the end of i.v. therapy, anidulafungin was superior to fluconazole in the treatment of patients with candidemia and/or other forms of invasive candidiasis. In the anidulafungin arm, 96 patients (75.6%) had global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (anidulafungin global success rate minus fluconazole global success rate) was 15.4% (95% CI: 3.9, 27.0).

Candida Infections in Neutropenic Patients
The efficacy of anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) in adult neutropenic patients (defined as absolute neutrophil count $\leq$500 cells/mm^3, WBC $\leq$500 cells/mm^3 or classified by the investigator as neutropenic at baseline) with microbiologically confirmed invasive candidiasis was assessed in an analysis of pooled data from 5 prospective studies (1 comparative versus caspofungin and 4 open-label, non-comparative). Patients were treated for at least 14 days. In clinically stable patients, a switch to oral azole therapy was permitted after at least 5 to 10 days of treatment with anidulafungin. A total of 46 patients were included in the analysis. The majority of patients had candidemia only (84.8%; 39/46). The most common pathogens isolated at baseline were *C. tropicalis* (34.8%; 16/46), *C. krusei* (19.6%; 9/46), *C. parapsilosis* (17.4%; 8/46), *C. albicans* (15.2%; 7/46), and *C. glabrata* (15.2%; 7/46). The successful global response rate at End of Intravenous Treatment (primary endpoint) was 26/46 (56.5%) and End of All Treatment was 24/46 (52.2%). All-cause mortality up to the end of the study (6 Week Follow-up Visit) was 21/46 (45.7%).

The efficacy of anidulafungin in adult neutropenic patients (defined as absolute neutrophil count $\leq$500 cells/mm^3 at baseline) with invasive candidiasis was assessed in a prospective, double-blind, randomized, controlled trial. Eligible patients received either anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily)

or caspofungin (70 mg intravenous loading dose followed by 50 mg intravenous daily) (2:1 randomization). Patients were treated for at least 14 days. In clinically stable patients, a switch to oral azole therapy was permitted after at least 10 days of study treatment. A total of 14 neutropenic patients with microbiologically confirmed invasive candidiasis (MITT population) were enrolled in the study (11 anidulafungin; 3 caspofungin). The majority of patients had candidemia only. The most common pathogens isolated at baseline were *C. tropicalis* (4 anidulafungin, 0 caspofungin), *C. parapsilosis* (2 anidulafungin, 1 caspofungin), *C. krusei* (2 anidulafungin, 1 caspofungin), and *C. ciferrii* (2 anidulafungin, 0 caspofungin). The successful global response rate at the End of Intravenous Treatment (primary endpoint) was 8/11 (72.7%) for anidulafungin and 3/3 (100.0%) for caspofungin (difference -27.3, 95% CI -80.9, 40.3); the successful global response rate at the End of All Treatment was 8/11 (72.7%) for anidulafungin and 3/3 (100.0%) for caspofungin (difference -27.3, 95% CI -80.9, 40.3). All-cause mortality up to the 6 Week Follow-Up visit for anidulafungin (MITT population) was 4/11 (36.4%) and 2/3 (66.7%) for caspofungin.

Patients with microbiologically confirmed invasive candidiasis (MITT population) and neutropenia were identified in an analysis of pooled data from 4 similarly designed prospective, open-label, non-comparative studies. The efficacy of anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) was assessed in 35 adult neutropenic patients defined as absolute neutrophil count $\leq$500 cells/mm^3 or WBC $\leq$500 cells/mm^3 in 22 patients or classified by the investigator as neutropenic at baseline in 13 patients. All patients were treated for at least 14 days. In clinically stable patients, a switch to oral azole therapy was permitted after at least 5 to 10 days of treatment with anidulafungin. The majority of patients had candidemia only (85.7%). The most common pathogens isolated at baseline were *C. tropicalis* (12 patients), *C. albicans* (7 patients), *C. glabrata* (7 patients), *C. krusei* (7 patients), and *C. parapsilosis* (6 patients). The successful global response rate at the End of Intravenous Treatment (primary endpoint) was 18/35 (51.4%) and 16/35 (45.7%) at the End of All Treatment. All-cause mortality by Day 28 was 10/35 (28.6%). The successful global response rate at End of Intravenous Treatment and End of All Treatment were both 7/13 (53.8%) in the 13 patients with neutropenia assessed by investigators at baseline.

Deep Tissue Infections

The efficacy of anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) in adult patients with microbiologically confirmed deep tissue candidiasis was assessed in an analysis of pooled data from 5 prospective studies (1 comparative and 4 open-label). Patients were treated for at least 14 days. In the 4 open-label studies, a switch to oral azole therapy was permitted after at least 5 to 10 days of treatment with anidulafungin. A total of 129 patients were included in the analysis. Twenty one (16.3%) had concomitant candidemia. The mean APACHE II score was 14.9 (range, 2 – 44). The most common sites of infection included the peritoneal cavity (54.3%; 70 of 129), hepatobiliary tract (7.0%; 9 of 129), pleural cavity (5.4%; 7 of 129) and kidney (3.1%; 4 of 129). The most common pathogens isolated from a deep tissue site at baseline were *C. albicans* (64.3%; 83 of 129), *C. glabrata* (31.0%; 40 of 129), *C. tropicalis* (11.6%; 15 of 129), and *C. krusei* (5.4%; 7 of 129). The successful global

response rate at the end of intravenous treatment (primary endpoint) and end of all treatment and all-cause mortality up to the 6 week follow-up visit is shown in Table 1.

Table 1: Rate of Successful Global Response[a] and All-Cause Mortality in Patients with Deep Tissue Candidiasis – Pooled Analysis

	MITT Population n/N (%)
Global Response of Success at EOIVT[b]	
Overall	102/129 (79.1)
Peritoneal cavity	51/70 (72.9)
Hepatobiliary tract	7/9 (77.8)
Pleural cavity	6/7 (85.7)
Kidney	3/4 (75.0)
Global Response of Success at EOT[b]	94/129 (72.9)
All-Cause Mortality	40/129 (31.0)

[a] A successful global response was defined as both clinical and microbiologic success
[b] EOIVT, End of Intravenous Treatment; EOT, End of All Treatment

Esophageal candidiasis
Anidulafungin was evaluated in a double-blind, double-dummy, randomized Phase 3 study. Patients were randomized to receive anidulafungin, once daily IV (100 mg loading dose followed by 50 mg/day) or oral fluconazole (200 mg loading dose 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, 91% had *C. albicans* isolated at the baseline. Treatment groups were similar in demographic and other baseline characteristics. In this study, of 280 patients tested, 237 (84.6%) tested HIV positive. In both groups the median time to resolution of symptoms was 5 days and the median duration of therapy was 14 days.

The primary endpoint was endoscopic outcome at end of therapy (EOT). Patients were considered clinically evaluable if they received at least 10 days of therapy, had an EOT assessment with a clinical outcome other than 'indeterminate', had an endoscopy at EOT, and did not have any protocol violations prior to the EOT visit that would affect an assessment of efficacy. An endoscopic success, defined as cure (endoscopic grade of 0 on a 4 point severity scale) or improvement (decrease of one or more grades from baseline), was seen in 225/231 (97.4%) anidulafungin-treated patients and 233/236 (98.7%) fluconazole-treated patients. The majority of these patients were endoscopic cures (grade=0). The between group difference in global success rate (anidulafungin minus fluconazole) was –1.3% (95% CI: -3.8,1.2).

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. The between group treatment difference (anidulafungin minus fluconazole) was 34% (95% CI: 25.8.42.3).

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.

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 candidemia (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 1, 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 2.

Table 2: Summary of Successful Global Response by Age Group, MITT Population Successful Global Response, n (%)

Timepoint	Global Response	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 All Treatment; FU = follow-up; MITT = modified intent-to-treat; N = number of subjects in the population; n = number of subjects with responses

5.2. Pharmacokinetic Properties

General Pharmacokinetic Characteristics
The pharmacokinetics of anidulafungin have been characterized in healthy subjects, special populations and patients. A low intersubject variability in systemic exposure (coefficient of variation of approximately 25%) was observed. The steady state was achieved on the first day after a loading dose (twice the daily maintenance dose).

Distribution
The pharmacokinetics of anidulafungin are characterized by a rapid distribution half-life (0.5-1 hour) and a volume of distribution of 30-50 L that is similar to total body fluid volume. Anidulafungin is extensively bound (>99%) to human plasma proteins.

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

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

Elimination
The clearance of anidulafungin is about 1 L/h. Anidulafungin has a predominant elimination half-life of approximately 24 hours that characterizes the majority of the plasma concentration-time profile and a terminal half-life of 40-50 hours that characterizes the terminal elimination phase of the profile.

In a single-dose clinical study, radiolabeled (^{14}C) anidulafungin (~88 mg) was administered to healthy subjects. Approximately 30% of the administered radioactive dose was eliminated in the 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

Patients with fungal infections
The pharmacokinetics of anidulafungin in patients with fungal infections are similar to those observed in healthy subjects based on population pharmacokinetic analyses. With the 200/100 mg daily dose regimen at an infusion rate of 1 mg/min, the steady state C_{max} and trough concentrations C_{min} could reach approximately 7 and 3 mg/L, respectively, with an average steady state AUC of approximately 110 mg·h/L.

Weight
Though weight was identified as a source of variability in clearance in the population pharmacokinetic analysis, weight has little clinical relevance on the pharmacokinetics of anidulafungin.

Gender
Plasma concentrations of anidulafungin in healthy men and women were similar. In multiple-dose patient studies, drug clearance was slightly faster (approximately 22%) in men.

Elderly
The population pharmacokinetic analysis showed that median clearance differed slightly between the elderly group (patients ≥65, median CL = 1.07 L/h) and the non-elderly group (patients <65, median CL = 1.22 L/h), however, the range of clearance was similar.

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

HIV Positivity
Dosage adjustments are not required based on HIV positivity, 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 a slight decrease in AUC was observed in patients with Child-Pugh C hepatic insufficiency, the decrease was within the range of population estimates noted for healthy subjects.

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.

Pediatric
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 **5.1 Pharmacodynamic Properties**). 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.

5.3. Preclinical Safety Data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, and toxicity to reproduction. In 3 month studies, evidence of liver toxicity, including elevated enzymes and morphologic alterations, was observed in both rats and monkeys at doses 4 to 6-fold higher than the anticipated clinical therapeutic exposure. *In vitro* and *in vivo* genotoxicity studies with anidulafungin provided no evidence of genotoxic potential. Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of anidulafungin.

Administration of anidulafungin to rats did not indicate any effects on reproduction, including male and female fertility.

Anidulafungin crossed the placental barrier in rats and was detected in fetal plasma. The potential risk to the human fetus is unknown.

Anidulafungin was found in the milk of lactating rats. It is not known whether anidulafungin is excreted in human milk.

Anidulafungin did not produce any drug-related developmental toxicity in rats at the highest dose of 20 mg/kg/day, a dose equivalent to 2 times the proposed therapeutic maintenance dose of 100 mg on the basis of relative body surface area. Developmental effects observed in rabbits (slightly reduced fetal weights) occurred in the high dose group, a dose that also produced maternal toxicity.

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.

Studies conducted in juvenile rats did not indicate a greater susceptibility to anidulafungin hepatotoxicity compared to adult animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Fructose
Mannitol (E421)
Polysorbate 80 (E433)
Tartaric acid (E334)
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

6.2. Shelf-Life

Powder: Please see outer package for the expiration date.

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

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.

Infusion Solution:
The infusion solution may be stored at 25°C for 48 hours
Do not freeze.

Chemical and physical in-use stability of the infusion solution has been demonstrated for 48 hours at 25°C.

From a microbiological point of view, following good aseptic practices, the infusion solution can be utilized for up to 48 hours from the preparation when stored at 25°C.

6.3. Storage Conditions

For storage conditions of the reconstituted and diluted medicinal product, see section **6.2 Shelf Life.**

Store medicinal product in a refrigerator (2°C-8°C). Excursions for 96 hours up to 25°C are permitted, and the powder can be returned to refrigerated storage.

6.4. Availability

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. Box of 1's.

6.5. Incompatibilities

This medicinal product must not be mixed or co-administered with other medicinal products or electrolytes except those mentioned in section **6.6 Special Precautions for Disposal and Other Handling**.

6.6. Special Precautions for Disposal and Other Handling

Anidulafungin must be reconstituted with sterile water for injection and subsequently diluted with ONLY 9 mg/mL (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion. The compatibility of reconstituted anidulafungin with intravenous substances, additives, or medications other than 9 mg/mL (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion has not been established. The infusion solution must not be frozen.

Reconstitution of Water for Injection Presentation
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.

The reconstituted solution may be stored at up to 25°C for 24 hours.

Dilution and Infusion of Water for Injection Presentation

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 an IV bag (or bottle) containing either 9 mg/mL (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion to obtain the appropriate anidulafungin concentration. The table below provides the volumes required for each dose dilution to a concentration of 0.77 mg/mL for the final infusion solution and infusion instructions for each dose.

Dilution Requirements for Anidulafungin Administration of Water for Injection Presentation

Dose	Number of Unit Packs Required	Total Reconstituted Volume Required	Infusion Volume[A]	Total Infusion Volume[B]	Rate of Infusion	Minimum Duration of Infusion
100 mg	1-100 mg	30 mL	100 mL	130 mL	1.4 mL/min or 84 mL/hour	90 min
200 mg	2-100 mg	60 mL	200 mL	260 mL	1.4 mL/min or 84 mL/hour	180 min

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

The rate of infusion should not exceed 1.1 mg/minute (see sections **4.4 Special Warnings and Precautions for Use** and **4.8 Undesirable Effects**). The rate of infusion is equivalent to 1.4 mL/min or 84 mL/hour for the 100 mg dose.

Pediatric Patients

For pediatric patients aged 1 month to < 18 years, the volume of infusion solution required to deliver the dose will vary depending on the weight of the patient. The reconstituted solution must be further diluted to a concentration of 0.77 mg/mL for the final infusion solution. A programmable syringe or infusion pump is recommended. **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 sections **4.2 Dosage and Method of Administration** and **4.4 Special Warnings and Precautions for Use**).

1. Calculate patient dose and reconstitute vial(s) required according to reconstitution instructions to provide a concentration of 3.33 mg/mL (see sections **3 Formulation/Composition** and **4.2 Dosage and Method of Administration**)

2. Calculate the volume (mL) of reconstituted anidulafungin required:

   - Volume of anidulafungin (mL) = Dose of anidulafungin (mg) ÷ 3.33 mg/mL

3. Calculate the total volume of dosing solution (mL) required to provide a final concentration of 0.77 mg/mL:

   - Total volume of dosing solution (mL) = Dose of anidulafungin (mg) ÷ 0.77 mg/mL

4. Calculate the volume of diluent [5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline)] required to prepare the dosing solution:

• Volume of diluent (mL) = Total volume of dosing solution (mL) – Volume of anidulafungin (mL)

5. Aseptically transfer the required volumes (mL) of anidulafungin and 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline) into an infusion syringe or IV infusion bag needed for administration.

   For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. FDA REGISTRATION NUMBER

100 mg Lyophilized Powder for Injection (IV Infusion): DR-XY38322

8. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

100 mg Lyophilized Powder for Injection (IV Infusion): 22 May 2007

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Acts Prohibits dispensing without prescription.

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