

## **ERAXIS**

### **Anidulafungin**

[INTRAVENOUS INFUSION, DILUTED WITH STERILE WATER FOR INJECTION]

(not for IV Bolus Injection)

#### **1. NAME OF THE MEDICINAL PRODUCT**

ERAXIS 100 mg powder for concentrate for solution for infusion

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains 100 mg anidulafungin.

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

#### **3. PHARMACEUTICAL FORM**

Powder for concentrate for solution for infusion.

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic Indications**

Treatment of invasive candidiasis in adult patients (see sections 4.4 and 5.1).

##### **4.2 Posology and Method of Administration**

Treatment with ERAXIS should be initiated by a physician experienced in the management of invasive fungal infections. Specimens for fungal culture should be obtained prior to therapy. Therapy may be initiated before culture results are known and can be adjusted accordingly once they are available.

##### Posology

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.

##### *Duration of treatment*

There are insufficient data to support the 100 mg dose for longer than 35 days of treatment.

##### *Patients with 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. ERAXIS can be given without

regard to the timing of haemodialysis (see section 5.2).

#### *Other special populations*

No dosing adjustments are required for adult patients based on gender, weight, ethnicity, HIV positivity, or elderly (see section 5.2).

#### *Paediatric population*

The safety and efficacy of ERAXIS in children below 18 years have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

#### Method of administration

For intravenous use only.

ERAXIS should be reconstituted with water for injections to a concentration of 3.33 mg/mL and subsequently diluted to a concentration of 0.77 mg/mL. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

It is recommended that ERAXIS be administered at a rate of infusion that does not exceed 1.1 mg/min (equivalent to 1.4 mL/min when reconstituted and diluted per instructions).

Infusion associated reactions are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/min (see section 4.4).

ERAXIS must not be administered as a bolus injection.

### **4.3 Contraindications**

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

Hypersensitivity to other medicinal products of the echinocandin class.

### **4.4 Special Warnings and Precautions for Use**

ERAXIS has not been studied in patients with *Candida endocarditis*, osteomyelitis or meningitis.

The efficacy of ERAXIS has only been evaluated in a limited number of neutropenic patients (see section 5.1).

#### Hepatic effects

Increased levels of hepatic enzymes have been seen in healthy subjects and patients treated with anidulafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medicines along with anidulafungin, clinically significant hepatic abnormalities have occurred. Cases of significant hepatic dysfunction, hepatitis, and hepatic failure were uncommon in clinical trials. Patients with increased hepatic enzymes during anidulafungin therapy

should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.

#### Anaphylactic reactions

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

#### 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/min.

Exacerbation of infusion-related reactions by co-administration of anaesthetics has been seen in a non-clinical (rat) study (see section 5.3). The clinical relevance of this is unknown. Nevertheless, care should be taken when co-administering anidulafungin and anaesthetic agents.

#### Fructose content

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

### **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**

Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A). Of note, *in vitro* studies do not fully exclude possible *in vivo* interactions.

Drug interaction studies were performed with anidulafungin and other medicinal products likely to be co-administered. No dosage adjustment of either medicinal product is recommended when anidulafungin is co-administered with ciclosporin, voriconazole or tacrolimus, and no dosage adjustment for anidulafungin is recommended when co-administered with amphotericin B or rifampicin.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, Pregnancy and Lactation**

#### Pregnancy

There are no data regarding the use of anidulafungin in pregnant women. Slight developmental effects have been observed in rabbits administered anidulafungin during pregnancy, in the presence of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore anidulafungin is not recommended in pregnancy.

#### Breast-feeding

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 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.

#### Fertility

For anidulafungin, there were no effects on fertility in studies conducted in male and female rats (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**

##### Summary of the safety profile

Fifteen hundred sixty five (1565) subjects received single or multiple doses of intravenous anidulafungin in clinical trials: 1308 in Phase 2/3 trials (923 patients with candidaemia/invasive candidiasis, 355 patients with oral/oesophageal candidiasis, 30 patients with invasive aspergillosis), and 257 in Phase I studies.

The safety profile of anidulafungin is based on 840 patients with candidaemia/invasive candidiasis receiving the recommended daily dose of 100 mg in 9 studies. Originally, in 3 studies (one comparative vs. fluconazole, two non-comparative) 204 patients were studied; the mean duration of intravenous treatment in these patients was 13.5 days (range, 1 to 38 days) and 119 patients received  $\geq 14$  days of anidulafungin. In 6 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 reactions were typically mild to moderate and seldom led to discontinuation.

Infusion-related adverse reactions have been reported with anidulafungin in clinical studies, including flushing, hot flush, pruritus, rash, and urticaria, summarized in Table 1.

##### Tabulated list of adverse reactions

The following table includes, the all-causality adverse reactions (MedDRA terms) from 840 subjects receiving 100 mg anidulafungin with frequency corresponding to very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and from spontaneous reports with frequency not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1. Table of Adverse Reactions**

<b>System Organ Class</b>	<b>Very Common ≥1/10</b>	<b>Common ≥1/100 to &lt;1/10</b>	<b>Uncommon ≥1/1000 to &lt;1/100</b>	<b>Rare ≥ 1/10,000 to &lt;1/1,000</b>	<b>Very Rare &lt;1/10,000</b>	<b>Not Known</b>
Blood and Lymphatic System Disorders			Coagulopathy			
Immune System Disorders						Anaphylactic shock, anaphylactic reaction*
Metabolism and Nutrition Disorders	Hypokalaemia	Hyperglycaemia				
Nervous System Disorders		Convulsion, headache				
Vascular Disorders		Hypotension, hypertension	Flushing, hot flush			
Respiratory, Thoracic and Mediastinal Disorders		Bronchospasm, Dyspnoea				
Gastrointestinal Disorders	Diarrhoea, nausea	Vomiting	Abdominal pain upper			
Hepatobiliary Disorders		Alanine aminotransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, cholestasis	Gamma-glutamyltransferase increased			
Skin and Subcutaneous Tissue Disorders		Rash, pruritus	Urticaria			
Renal and Urinary Disorders		Blood creatinine increased				
General Disorders and Administration Site Conditions			Infusion site pain			

\* See section 4.4.

## 4.9 Overdose

As with any overdose, general supportive measures should be utilised as necessary. In case of overdose, adverse reactions may occur as mentioned in section 4.8.

During clinical trials, a single 400 mg dose of anidulafungin was inadvertently administered as a loading dose. No clinical adverse reactions were reported. No dose limiting toxicity was observed 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 ( $\leq 3 \times$  Upper Limit of Normal (ULN)).

ERAXIS is not dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: – Antimycotics for systemic use, other antimycotics for systemic use. ATC code: JO2AX06

#### Mechanism of action

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

Anidulafungin selectively inhibits 1,3- $\beta$ -D glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3- $\beta$ -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 exhibited *in-vitro* activity against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei* and *C. tropicalis*. For the clinical relevance of these findings see “Clinical efficacy and safety.”

Isolates with mutations in the hot spot regions of the target gene have been associated with clinical failures or breakthrough infections. Most clinical cases involve caspofungin treatment. However, in animal experiments these mutations confer cross resistance to all three echinocandins and therefore such isolates are classified as echinocandin resistant until further clinical experience are obtained concerning anidulafungin.

The *in vitro* activity of anidulafungin against *Candida* species is not uniform. Specifically, for *C. parapsilosis*, the MICs of anidulafungin are higher than are those of other *Candida* species. A standardized technique for testing the susceptibility of *Candida* species to anidulafungin as well as the respective interpretative breakpoints has been established by European Committee on Antimicrobial Susceptibility Testing (EUCAST).

**Table 2. EUCAST Breakpoints**

<u>Candida Species</u>	<u>MIC breakpoint (mg/L)</u>	
	<u>≤S (Susceptible)</u>	<u>&gt;R (Resistant)</u>
<i>Candida albicans</i>	0.03	0.03
<i>Candida glabrata</i>	0.06	0.06
<i>Candida tropicalis</i>	0.06	0.06
<i>Candida krusei</i>	0.06	0.06
<i>Candida parapsilosis</i> <sup>1</sup>	0.002	4
Other <i>Candida</i> spp. <sup>2</sup>	Insufficient evidence	

<sup>1</sup>*C. parapsilosis* harbours an intrinsic alteration in the target gene, which is the likely mechanism for the higher MICs than with other *Candida* species. In the clinical trials the outcome for anidulafungin with *C. parapsilosis* was not statistically different from other species however, the use of echinocandins in candidaemia due to *C. parapsilosis* may not be regarded as therapy of first choice

<sup>2</sup> EUCAST has not determined non-species related breakpoints for anidulafungin

### Activity in vivo

Parenterally administered anidulafungin was effective against *Candida* species in immunocompetent and immunocompromised mouse and rabbit models. Anidulafungin treatment prolonged survival and also reduced the organ burden of *Candida* species, when determined at intervals from 24 to 96 hours after the last treatment.

Experimental infections included disseminated *C. albicans* infection in neutropenic rabbits, oesophageal/oropharyngeal infection of neutropenic rabbits with fluconazole-resistant *C. albicans* and disseminated infection of neutropenic mice with fluconazole-resistant *C. glabrata*.

### Clinical efficacy and safety

#### *Candidaemia and other forms of Invasive Candidiasis*

The safety and efficacy of anidulafungin were evaluated in a pivotal Phase 3, randomised, double-blind, multicentre, multinational study of primarily non-neutropenic patients with candidaemia and a limited number of patients with deep tissue *Candida* infections or with abscess-forming disease. Patients with *Candida* endocarditis, osteomyelitis or meningitis, or those with infection due to *C. krusei*, were specifically excluded from the study. Patients were randomised to receive either anidulafungin (200 mg intravenous loading dose followed by 100 mg intravenous daily) or fluconazole (800 mg intravenous loading dose followed by 400 mg intravenous daily), and were stratified by APACHE II score ( $\leq 20$  and  $> 20$ ) and the presence or absence of neutropaenia. 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 and were afebrile for at least 24 hours, and that 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 study entry were included in the modified intent-to-treat (MITT) population. In the primary efficacy analysis, global response in the MITT populations at the end of intravenous therapy, anidulafungin was compared to fluconazole in a pre-specified two-step statistical comparison (non-inferiority followed by superiority). 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, ranging from 16 to 91 years in age, were randomised to treatment and received at least one dose of study medication. 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%) - with 20, 13 and 15 isolates of the last 3 species, respectively, in the anidulafungin group. The majority of patients had Apache II scores  $\leq 20$  and very few were neutropenic.

Efficacy data, both overall and by various subgroups, are presented below in Table 3.

<b>Table 3. Global success in the MITT population: primary and secondary endpoints</b>			
	Anidulafungin	Fluconazole	Between group difference <sup>a</sup> (95% CI)
<b>End of IV Therapy (1<sup>o</sup> endpoint)</b>	<b>96/127 (75.6%)</b>	<b>71/118 (60.2%)</b>	<b>15.42 (3.9, 27.0)</b>
Candidaemia only	88/116 (75.9%)	63/103 (61.2%)	14.7 (2.5, 26.9)
Other sterile sites <sup>b</sup>	8/11 (72.7%)	8/15 (53.3%)	-
Peritoneal fluid/IA <sup>c</sup> abscess	6/8	5/8	
Other	2/3	3/7	
<i>C. albicans</i> <sup>d</sup>	60/74 (81.1%)	38/61 (62.3%)	-
Non- <i>albicans</i> species <sup>d</sup>	32/45 (71.1%)	27/45 (60.0%)	-
Apache II score $\leq 20$	82/101 (81.2%)	60/98 (61.2%)	-
Apache II score $> 20$	14/26 (53.8%)	11/20 (55.0%)	-
Non-neutropenic (ANC, cells/mm <sup>3</sup> $> 500$ )	94/124 (75.8%)	69/114 (60.5%)	-
Neutropenic (ANC, cells/mm <sup>3</sup> $\leq 500$ )	2/3	2/4	-
<b>At Other Endpoints</b>			
End of All Therapy	94/127 (74.0%)	67/118 (56.8%)	17.24 (2.9, 31.6) <sup>e</sup>
2 Week Follow-up	82/127 (64.6%)	58/118 (49.2%)	15.41 (0.4, 30.4) <sup>e</sup>
6 Week Follow-up	71/127 (55.9%)	52/118 (44.1%)	11.84 (-3.4, 27.0) <sup>e</sup>

<sup>a</sup> Calculated as anidulafungin minus fluconazole.

<sup>b</sup> With or without concurrent candidaemia.

<sup>c</sup> Intra-abdominal.

<sup>d</sup> Data presented for patients with a single baseline pathogen.

<sup>e</sup> 98.3% confidence intervals, adjusted post hoc for multiple comparisons of secondary time points.

Mortality rates in both the anidulafungin and fluconazole arms are presented below in Table 4:

<b>Table 4. Mortality</b>		
	Anidulafungin	Fluconazole
<b>Overall study mortality</b>	<b>29/127 (22.8%)</b>	<b>37/118 (31.4%)</b>
Mortality during study therapy	10/127 (7.9%)	17/118 (14.4%)
Mortality attributed to <i>Candida</i> infection	2/127 (1.6%)	5/118 (4.2%)

#### **Additional data 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<sup>3</sup>, WBC  $\leq 500$  cells/mm<sup>3</sup> 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<sup>3</sup> 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<sup>3</sup> or WBC  $\leq 500$  cells/mm<sup>3</sup> 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.

### **Additional data in patients with 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 5.

**Table 5. Rate of Successful Global Response<sup>a</sup> and All-Cause Mortality in Patients with Deep Tissue Candidiasis – Pooled Analysis**

	MITT Population n/N (%)
<b>Global Response of Success at EOIVT<sup>b</sup></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)
<b>Global Response of Success at EOT<sup>b</sup></b>	94/129 (72.9)
<b>All-Cause Mortality</b>	40/129 (31.0)

<sup>a</sup> A successful global response was defined as both clinical and microbiologic success

<sup>b</sup> EOIVT, End of Intravenous Treatment; EOT, End of All Treatment

## **5.2 Pharmacokinetic Properties**

### General pharmacokinetic characteristics

The pharmacokinetics of anidulafungin have been characterised in healthy subjects, special populations and patients. A low intersubject variability in systemic exposure (coefficient of variation ~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 characterised by a rapid distribution half-life (0.5-1 hour) and a volume of distribution, 30-50 L, which is similar to total body fluid volume. Anidulafungin is extensively bound (>99%) to human plasma proteins. No specific tissue distribution studies of anidulafungin have been done in humans. Therefore, no information is available about the penetration of anidulafungin into the cerebrospinal fluid (CSF) and/or across the blood-brain barrier.

### 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 metabolised 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 characterises the terminal elimination phase of the profile.

In a single-dose clinical study, radiolabeled (<sup>14</sup>C) anidulafungin (~88 mg) was administered to healthy subjects. Approximately 30% of the administered radioactive dose was eliminated in the faeces over 9 days, of which less than 10% was intact drug. Less than 1% of the administered radioactive dose was excreted in the urine, indicating negligible renal clearance. 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 faeces 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 1.1 mg/min, the steady-state C<sub>max</sub> and trough concentrations (C<sub>min</sub>) could reach approximately 7 and 3 mg/L, respectively, with an average steady state AUC of approximately 110 mg·h/L.

#### *Weight*

Although 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  $\geq 65$ , 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 metabolised. 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 dialysable and may be administered without regard to the timing of hemodialysis.

### *Paediatric*

The pharmacokinetics of anidulafungin after at least 5 daily doses were investigated in 24 immunocompromised paediatric (2 to 11 years old) and adolescent (12 to 17 years old) patients with neutropenia. Steady state was achieved on the first day after a loading dose (twice the maintenance dose), and steady state  $C_{max}$  and  $AUC_{ss}$  increase in a dose-proportional manner. Systemic exposure following daily maintenance dose of 0.75 and 1.5 mg/kg/day in this population were comparable to those observed in adults following 50 and 100 mg/day, respectively. Both regimens were well-tolerated by these patients.

## **5.3 Preclinical Safety Data**

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 foetal plasma.

Embryo-foetal development studies were conducted with doses between 0.2- and 2-fold (rats) and between 1- and 4-fold (rabbits) the proposed therapeutic maintenance dose of 100 mg/day. Anidulafungin did not produce any drug-related developmental toxicity in rats at the highest dose tested. Developmental effects observed in rabbits (slightly reduced foetal weights) occurred only at the highest dose tested, a dose that also produced maternal toxicity.

The concentration of anidulafungin in the brain was low (brain to plasma ratio of approximately 0.2) in uninfected adult and neonatal rats after a single dose. However, brain concentrations increased in uninfected neonatal rats after five daily doses (brain to plasma ratio of approximately 0.7). In multiple dose studies in rabbits with disseminated candidiasis and in mice with CNS candida infection, anidulafungin has been shown to reduce fungal burden in the brain.

Rats were dosed with anidulafungin at three dose levels and anaesthetised within one hour using a combination of ketamine and xylazine. Rats in the high dose group experienced infusion-related reactions that were exacerbated by anaesthesia. Some rats in the mid dose group experienced similar reactions but only after administration of anaesthesia. There were no adverse reactions in the low-dose animals in the presence or absence of anaesthesia, and no infusion-related reactions in the mid-dose group in the absence of anaesthesia.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 Incompatibilities**

This medicinal product must not be mixed with other medicinal products or electrolytes except those mentioned in section 6.4.

### **6.2 Shelf-life**

Please refer to carton for shelf life.

### **6.3 Special Precautions for Storage**

#### Unreconstituted vials

Store in a refrigerator at 2°C – 8°C. Do not freeze.

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

#### Reconstituted solution

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

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours when stored 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 can be stored at temperatures 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 preparation when stored at 25°C.

### **6.4 Special Precautions for Disposal and Other Handling**

ERAXIS must be reconstituted with water for injections and subsequently diluted with ONLY 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline). The compatibility of reconstituted ERAXIS with intravenous substances, additives, or medicines other than 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (normal saline) has not been established. The infusion solution must not be frozen.

#### Reconstitution

Aseptically reconstitute each vial with 30 mL water for injections to provide a concentration of 3.33 mg/mL. After subsequent dilution, the solution is to be discarded if particulate matter or discoloration is identified.

#### Dilution and infusion

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

#### Dilution requirements for ERAXIS administration

<b>Dose</b>	<b>Number of vials of powder</b>	<b>Total reconstituted volume</b>	<b>Infusion volume<sup>A</sup></b>	<b>Total infusion volume<sup>B</sup></b>	<b>Rate of infusion</b>	<b>Minimum duration of infusion</b>
100 mg	1	30 mL	100 mL	130 mL	1.4 mL/min	90 min
200 mg	2	60 mL	200 mL	260 mL	1.4 mL/min	180 min

<sup>A</sup> Either 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP.

<sup>B</sup> Infusion solution concentration is 0.77 mg/mL

The rate of infusion should not exceed 1.1 mg/min (equivalent to 1.4 mL/min when reconstituted and diluted per instructions) (see sections 4.2, 4.4 and 4.8).

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

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