SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Anidulafungin 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.

Excipient(s) with known effect:
Each vial contains 250 mg polysorbate 80 (E 433) which is equivalent to 3.6 mg/kg for adult population (e.g. 70 kg body weight).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White to off white powder, free of visible evidence of contamination
The reconstituted solution has a pH of 3.5 to 5.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of invasive candidiasis in adults and paediatric patients aged 1 month to < 18 years (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with Anidulafungin should be initiated by a physician experienced in the

management of invasive fungal infections.

Posology

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.

Adult population (dosing and treatment duration)
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

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. Anidulafungin 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 (1 month to < 18 years) (dosing and treatment duration)
A single loading dose of 3.0 mg/kg (not to exceed 200 mg) should be administered on Day 1 followed by a daily maintenance dose of 1.5 mg/kg (not to exceed 100 mg) 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.

The safety and efficacy of anidulafungin have not been established in neonates (< 1 month old) (see section 4.4).

Method of administration

For intravenous use only.

Anidulafungin 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 the final infusion solution. For a paediatric patient, the volume of infusion solution required to deliver the dose will vary depending on the weight of the child. For instructions on reconstitution of the medicinal product before administration, see section 6.6. The appearance after reconstitution is a clear, colourless to yellow solution.

It is recommended that Anidulafungin 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).

Anidulafungin must not be administered as a bolus injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Hypersensitivity to other medicinal products of the echinocandin class.

4.4 Special warnings and precautions for use

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

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

Paediatric population

Treatment with anidulafungin in neonates (< 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), resulting in higher doses of polysorbate 80, a formulation excipient. High doses of polysorbates have been associated with potentially life-threatening toxicities in neonates as reported in the literature.

There is no clinical data to support the efficacy and safety of higher doses of anidulafungin than recommended in 4.2.

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, dyspnoea, bronchospasm and hypotension. Infusion-related adverse events are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/min (see section 4.8).

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.

Excipient(s)

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Anidulafungin may be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Polysorbate
Polysorbates may cause allergic reactions.
Polysorbates can have an effect on the heart and blood circulation (e.g., irregular or abnormal heartbeat, or low blood pressure). Risk minimization by lowering the rate of infusion is to be considered.
Due to a potential for QT prolongation and torsades de pointes of polysorbates in humans, there is a risk of concomitant use of medications that prolong the QT/QTc interval and in patients with congenital syndrome.

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 from the use of anidulafungin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Anidulafungin is not recommended during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether anidulafungin is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of anidulafungin in milk.

A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from anidulafungin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

Infusion-related adverse reactions have been reported with anidulafungin in clinical studies, including rash, pruritus, dyspnoea, bronchospasm, hypotension (common events), flushing, hot flush, and urticaria (uncommon events), summarized in Table 1 (see section 4.4).

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 (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥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

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon 1/1000 to <1/100**	**Rare ≥ 1/10,000 to <1/1,000**	**Very Rare < 1/10,000**	**Not Known**
Blood and Lymphatic System			Coagulopathy			
Immune System Disorders						Anaphylactic shock, anaphyla
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-glutamyltrans ferase 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.

Paediatric population

The safety of anidulafungin was investigated in 68 paediatric patients (1 month to < 18 years) with ICC in a prospective, open-label, non-comparative paediatric study (see section 5.1). The frequencies of certain hepatobiliary adverse events, including alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased appeared at a higher frequency (7-10%) in these paediatric patients than has been observed in adults (2%). Although chance or differences in underlying disease severity may have contributed, it cannot be excluded that hepatobiliary adverse reactions occur more frequently in paediatric patients compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

via the Yellow Card Scheme Website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 (≤3 x Upper Limit of Normal (ULN)).

During a paediatric 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

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use.
ATC code: J02AX06

Mechanism of action

Anidulafungin is a semi-synthetic echinocandin, a lipopeptide synthesised 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 *invitro*

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).

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for anidulafungin and are listed here: <https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx>

Activity *invivo*

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 (≤20 and >20) and the presence or absence of neutropenia. 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 medicinal products 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 medicinal products 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 ≤ 20 and very few were neutropenic.

Efficacy data, both overall and by various subgroups, are presented below in Table 2.

Table 2. Global success in the MITT population: primary and secondary endpoints

	Anidulafungin	Fluconazole	Between group difference [a] (95% CI)
End of IV Therapy (1º endpoint)	**96/127 (75.6%)**	**71/118 (60.2%)**	**15.42 (3.9, 27.0)**
Candidaemia only	88/116 (75.9%)	63/103 (61.2%)	14.7 (2.5, 26.9)
Other sterile sites[b]	8/11 (72.7%)	8/15 (53.3%)	-
Peritoneal fluid/IA[c] abscess	6/8	5/8	

Other	2/3	3/7	
C. albicans[d]	60/74 (81.1%)	38/61 (62.3%)	-
Non-*albicans* species[d]	32/45 (71.1%)	27/45 (60.0%)	-
Apache II score ≤ 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^3 > 500)**	94/124 (75.8%)	69/114 (60.5%)	-
Neutropenic **(ANC, cells/mm^3 ≤ 500)**	2/3	2/4	-
At Other Endpoints			
End of All Therapy	94/127 (74.0%)	67/118 (56.8%)	17.24 (2.9, 31.6)[e]
2 Week Follow-up	82/127 (64.6%)	58/118 (49.2%)	15.41 (0.4, 30.4)[e]
6 Week Follow-up	71/127 (55.9%)	52/118 (44.1%)	11.84 (-3.4, 27.0)[e]

[a] Calculated as anidulafungin minus fluconazole

[b] With or without concurrent candidaemia

[c] Intra-abdominal

[d] Data presented for patients with a single baseline pathogen.

[e] 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 3:

Table 3. Mortality		
	Anidulafungin	Fluconazole
Overall study mortality	**29/127 (22.8%)**	**37/118 (31.4%)**
Mortality during study therapy	10/127 (7.9%)	17/118 (14.4%)
Mortality attributed to *Candida* 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 ≤ 500 cells/mm^3, WBC ≤ 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 candidaemia 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 ≤ 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 candidaemia only. The most common pathogens isolated at baseline were *C. tropicalis* (4 anidulafungin, 0 caspofungin), *C. parapsilosi*s (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 ≤ 500 cells/mm^3 or WBC ≤ 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 candidaemia 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 candidaemia. 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 4.

Table 4. 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

Paediatric population

A prospective, open-label, non-comparative, multi-national study assessed the safety and efficacy of anidulafungin in 68 paediatric patients aged 1 month to < 18 years with invasive candidiasis including candidaemia (ICC). Patients were stratified by age (1 month to < 2 years, 2 to < 5 years, and 5 to < 18 years) and received once daily intravenous anidulafungin (3.0 mg/kg loading dose on Day 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 5.

Table 5. 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 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 (^{14}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_{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
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 ≥ 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 population
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.

The pharmacokinetics of anidulafungin was investigated in 66 paediatric patients (1 month to
< 18 years) with ICC in a prospective, open-label, non-comparative paediatric study following administration of 3.0 mg/kg loading dose and 1.5 mg/kg/day maintenance dose (see section 5.1). Based on population pharmacokinetic analysis of combined data from adult and paediatric patients with ICC, the mean exposure parameters (AUC0-24,ss and Cmin,ss) at steady state in the overall paediatric 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

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 central nervous system (CNS) Candida infection, anidulafungin has been shown to reduce fungal burden in the brain. 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 (see section 4.4).

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.

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

Sucrose
Polysorbate 80 (E 433)
Tartaric acid
Sodium hydroxide (E 524) (for pH adjustment)
Hydrochloric acid (E 507) (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or electrolytes except those mentioned in section 6.6.

6.3 Shelf life

3 years

Excursions for up to 96 hours at temperatures up to 25ºC are permitted, and the powder can be returned to refrigerated storage.

Reconstituted solution

The reconstituted solution may be stored at up to 25°C for up to 24 hours. Do not freeze.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25ºC.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

Infusion solution

The infusion solution may be stored at 25º C for 48 hours. Do not freeze.

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

25º C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2^{o} C – 8^{o} C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 colourless glass vial, closed with type 1 butyl rubber stopper and aluminium
metallic cap with polypropylene disk.

Pack size of 1 vial.

6.6 Special precautions for disposal

There are no special requirements for disposal.

Anidulafungin must be reconstituted with water for injections and subsequently diluted with ONLY sodium chloride 9 mg/mL (0.9%) solution for infusion or 50 mg/mL (5%) glucose for infusion. The compatibility of reconstituted Anidulafungin with intravenous substances, additives, or medicines 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

Aseptically reconstitute each vial with 30 mL water for injections to provide a concentration of

3.33 mg/mL. The reconstitution time can be up to 5 minutes. After subsequent dilution, the solution is to be discarded if particulate matter or discolouration is identified. The appearance after reconstitution is a clear, colourless to yellow solution.

Dilution and infusion

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

Adult Patients

Aseptically transfer the contents of the reconstituted vial(s) by adding slowly the solution into an intravenous bag (or bottle) containing either 9 mg/mL (0.9%) sodium chloride for infusion or 50 mg/mL (5%) glucose for infusion, with constant gentle agitation to obtain the appropriate anidulafungin concentration. The table below provides the 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

Dose	Number of vials of powder	Total reconstituted volume	Volume of infusion diluent [A]	Total infusion volume [B]	Rate of infusion	Minimum duration of infusion
100 mg	1	30 mL	100 mL	130 mL	1.4 mL/ min or 84 mL/hour	90 min
200 mg	2	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/min (equivalent to 1.4 mL/min or 84 mL/hour when reconstituted and diluted per instructions) (see sections 4.2, 4.4 and 4.8).

Paediatric Patients

For paediatric 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 and 4.4).

1. Calculate patient dose and reconstitute vial(s) required according to reconstitution instructions to provide a concentration of 3.33 mg/mL (see sections 2 and 4.2)

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 [sodium chloride 9 mg/mL (0.9%) solution for infusion or 50 mg/mL (5%) glucose for infusion] 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 sodium chloride 9 mg/mL (0.9%) solution for infusion or 50 mg/mL (5%) glucose for infusion 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 MARKETING AUTHORISATION HOLDER

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