ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ECALTA 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 with known effect: Fructose 102.5 mg per vial

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White to off-white lyophilised solid.
The reconstituted solution has a pH of 3.5 to 5.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of invasive candidiasis in adult non-neutropenic patients.

ECALTA has been studied primarily in patients with candidaemia and only in a limited number of patients with deep tissue *Candida* infections or with abscess-forming disease (see sections 4.4 and section 5.1).

4.2 Posology and method of administration

Treatment with ECALTA 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.

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. ECALTA 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 geriatric status (see section 5.2).

Paediatric population
The safety and efficacy of ECALTA 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.

ECALTA 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 before use according to the instructions given in section 6.6.

It is recommended that ECALTA be administered at a rate of infusion that does not exceed 1.1 mg/minute (equivalent to 1.4 ml/minute when reconstituted and diluted per instructions). Infusion associated reactions are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute (see section 4.4).

ECALTA 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

The efficacy of ECALTA in neutropenic patients with candidaemia and in patients with deep tissue *Candida* infections or intra-abdominal abscess and peritonitis has not been established.
Clinical efficacy has been evaluated primarily in non-neutropenic patients with *C. albicans* infections and in a smaller number of patients infected with non-albicans, mainly *C. glabrata*, *C. parapsilosis* and *C. tropicalis.* Patients with candida endocarditis, osteomyelitis or meningitis and known *C.krusei* infection have not been studied.

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/minute.

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.

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
Nine hundred and twenty-nine (929) subjects received single or multiple doses of intravenous anidulafungin in clinical trials: 672 in Phase 2/3 trials (287 patients with candidaemia/invasive candidiasis, 355 patients with oral/oesophageal candidiasis, 30 patients with invasive aspergillosis), and 257 in Phase I studies.

Three studies (one comparative vs fluconazole, two non-comparative) assessed the efficacy of anidulafungin in patients with candidaemia and a limited number of patients with deep tissue *Candida* infections. A total of 204 patients received the recommended daily dose of 100 mg; the mean duration of intravenous treatment in these patients was 13.5 days (range, 1 to 38 days). One hundred and nineteen patients received ≥ 14 days of anidulafungin. Adverse reactions were typically mild to moderate and seldom led to discontinuation.

Infusion-related adverse reactions have been reported with anidulafungin; in the pivotal ICC study, these included flushing/hot flush (2.3%), pruritus (2.3%), rash (1.5%), and urticaria (0.8%). Other treatment-related adverse reactions that occurred in ≥ 1% of patients in the pivotal study included hypokalaemia (3.1%), diarrhoea (3.1%), ALT increased (2.3%), hepatic enzyme increased (1.5%), blood alkaline phosphatase increased (1.5%), and blood bilirubin increased (1.5%).

Tabulated list of adverse reactions
The following table includes, the drug-related adverse reactions (MedDRA terms) from the 100 mg ICC database (N = 204), with frequency corresponding to common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100) 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 of Adverse Reactions

MedDRA System Organ Class	Frequency of Reported MedDRA Preferred Term		
	Common	**Uncommon**	**Not Known**
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	Flushing	Hypertension, hot flush	Hypotension
Respiratory , thoracic and mediastinal disorders	-	-	Bronchospasm, dyspnoea
Gastrointestinal disorders	Diarrhoea, vomiting, nausea	Abdominal pain upper	-
Hepatobiliary disorders	Alanine aminotransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased	Cholestasis	-
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 (≤3 x Upper Limit of Normal (ULN)).

ECALTA 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-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 exhibited *in-vitro* activity against *C. albicans, C. glabrata, C. parapsilosis,* and *C. tropicalis.* Susceptibility breakpoints for 1,3- β-D-glucan synthesis inhibitors have not been established. For the clinical relevance of these findings see below under clinical studies.

Minimum inhibitory concentration (MIC) determinations were performed according to the Clinical and Laboratory Standards Institute methods M27. 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., 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 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 ≤ 20 and very few were neutropenic.

Efficacy data, both overall and by various subgroups, are presented below in Table 1.

Table 1. 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 2:

Table 2. 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%)

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
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 List of excipients

Fructose
Mannitol
Polysorbate 80
Tartaric acid
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (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 96 hours 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.

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

From a microbiological point of view, following good aseptic practices, the reconstituted solution can be utilized for up to 24 hours when stored at 25ºC.

Infusion solution:
The infusion solution may be stored at 25ºC for 48 hours or stored frozen for at least 72 hours.

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

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 25ºC.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

6.5 Nature and contents of container

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 aluminium seal with flip-off cap.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

There are no special requirements for disposal.

ECALTA must be reconstituted with water for injections and subsequently diluted with ONLY sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose for infusion. The compatibility of reconstituted ECALTA 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.

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 discoloration is identified.

Dilution and infusion
Aseptically transfer the contents of the reconstituted vial(s) 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 obtaining an anidulafungin concentration of 0.77 mg/ml. The table below provides the volumes required for each dose.

Dilution requirements for ECALTA administration

Dose	Number of vials of powder	Total reconstituted volume	Infusion volume [A]	Total infusion volume[B]	Rate of infusion	Minimum duration of infusion
100 mg	1	30 ml	100 ml	130 ml	1.4 ml/ min	90 min
200 mg	2	60 ml	200 ml	260 ml	1.4 ml /min	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 (equivalent to 1.4 ml/minute 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 discolouration are identified, discard the solution.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/416/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs
The PSUR cycle for the medicinal product should follow a yearly cycle until otherwise agreed by the CHMP.

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ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

ECALTA 100 mg powder for concentrate for solution for infusion
Anidulafungin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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. LIST OF EXCIPIENTS

Excipients: fructose, mannitol, polysorbate 80, tartaric acid and NaOH and/or HCl for pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

Powder for concentrate for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute the contents with water for injections and dilute before use – read the package leaflet before use.
For intravenous use only.

Rate of infusion should not exceed 1.1 mg/minute

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MONTH – YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich
KENT
CT13 9NJ United-Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/416/002

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Justification for not including Braille accepted.]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ECALTA 100 mg powder for concentrate for solution for infusion
Anidulafungin
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

Store in a refrigerator

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ECALTA 100 mg powder for concentrate for solution for infusion
Anidulafungin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What ECALTA is and what it is used for

ECALTA contains the active substance anidulafungin and is prescribed in adults to treat a type of fungal infection of the blood or other internal organs called invasive candidiasis. The infection is caused by fungal cells (yeasts) called *Candida*.

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

ECALTA prevents normal development of fungal cell walls. In the presence of ECALTA, fungal cells have incomplete or defective cell walls, making them fragile or unable to grow.

2. What you need to know before you are treated with ECALTA

You should not be treated with ECALTA
- if you are allergic to anidulafungin, other echinocandins (e.g. CANCIDAS), or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Your doctor may decide to monitor
- your liver function more closely if you develop liver problems during your treatment.
- if you are given anaesthetics during your treatment with ECALTA.

Children

ECALTA should not be given to patients under 18 years of age.

Other medicines and ECALTA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not start or stop any other medicines without your doctor's or pharmacist's approval.

Pregnancy and breast-feeding

The effect of ECALTA in pregnant women is not known. Therefore ECALTA is not recommended during pregnancy. Effective contraception should be used in women of childbearing age. Contact your doctor immediately if you become pregnant while taking ECALTA.

The effect of ECALTA in breast-feeding women is not known. Ask your doctor or pharmacist for advice before taking ECALTA while breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicines.

ECALTA contains fructose

This medicine contains fructose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to use ECALTA

ECALTA will always be prepared and given to you by a doctor or a healthcare professional (there is more information about the method of preparation at the end of the leaflet in the section for medical and healthcare professionals only).

The treatment starts with 200 mg on the first day (loading dose). This will be followed by a daily dose of 100 mg (maintenance dose).

ECALTA should be given to you once a day, by slow infusion (a drip) into your vein. This will take at least 1.5 hours for the maintenance dose and 3 hours for the loading dose.

Your doctor will determine the duration of your treatment and how much ECALTA you will receive each day and will monitor your response and condition.

In general, your treatment should continue for at least 14 days after the last day *Candida* was found in your blood.

If you receive more ECALTA than you should

If you are concerned that you may have been given too much ECALTA, tell your doctor or another healthcare professional immediately.

If a dose of ECALTA has been forgotten

As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However tell your doctor or pharmacist if you think that a dose has been forgotten.

You should not be given a double dose by doctor.

Effects when treatment with ECALTA is stopped

You should not experience any effects from ECALTA if your doctor stops ECALTA treatment.

Your doctor may prescribe another medicine following your treatment with ECALTA to continue treating your fungal infection or prevent it from returning.

If your original symptoms come back, tell your doctor or another healthcare professional immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects will be noted by your doctor while monitoring your response and condition.

Life-threatening allergic reactions that might include difficulty breathing with wheezing or worsening of an existing rash have been rarely reported during administration of ECALTA.

Serious side effects – tell your doctor or another healthcare professional immediately should any of the following occur:
- Convulsion (seizure)
- Flushing
- Rash, pruritis (itching)
- Hot flush
- Hives
- Sudden contraction of the muscles around the airways resulting in wheezing or coughing
- Difficulty of breathing

Common side effects (may affect up to 1 in 10 people) are:

- Disorder of blood clotting system
- Low blood potassium (hypokalaemia)
- Convulsion (seizure)
- Headache
- Flushing
- Diarrhoea, vomiting, nausea
- Changes in blood tests of liver function
- Rash, pruritis (itching)
- Changes in blood tests of kidney function

Uncommon side effects (may affect up to 1 in 100 people) are:

- High blood sugar
- High blood pressure
- Hot flush
- Stomach pain
- Abnormal flow of bile from the gallbladder into the intestine (cholestasis)
- Hives
- Pain at injection site

Not known (frequency cannot be estimated from the available data) are:

- Low blood pressure
- Sudden contraction of the muscles around the airways resulting in wheezing or coughing
- Difficulty of breathing
- Life-threatening allergic reactions

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store ECALTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry data refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

The reconstituted solution may be stored up to 25°C for up to 24 hours. The infusion solution may be stored at 25°C (room temperature) for 48 hours or stored frozen for at least 72 hours, and should be administered at 25°C (room temperature) within 48 hours.

Do not throw away any medicines via wastewater or household waste.

6. Contents of the pack and other information

What ECALTA contains

- The active substance is anidulafungin. Each vial of powder contains 100 mg anidulafungin.
- The other ingredients are: fructose, mannitol, polysorbate 80, tartaric acid, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment)

What ECALTA looks like and contents of the pack

ECALTA is supplied as a box containing 1 vial of 100 mg powder for concentrate for solution for infusion.

The powder is white to off-white.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation for ECALTA is held by:
Pfizer Limited, Ramsgate Rd, Sandwich, Kent, CT13 9NJ, United Kingdom

Manufacturer

Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België /Belgique/Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

Luxembourg/Luxemburg
Pfizer S.A.
Tél: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Magyarország
Pfizer Kft.
Tel. + 36 1 488 37 00

Česká republika
Pfizer s.r.o.
Tel: +420-283-004-111

Malta
V.J. Salomone Pharma Ltd.
Tel : +356 21 22 01 74

Danmark
Pfizer ApS

Nederland
Pfizer bv

Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0) 30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 6 405 328

Ελλάδα
Pfizer Hellas A.E.
Τηλ: +30 210 6785 800

España
Pfizer S.A.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
Tel: +44 (0)1304 616161

Ísland
Icepharma hf.,
Sími: + 354 540 8000

Italia
Pfizer Italia S.r.l.
Tel: +39 06 33 18 21

Κύπρος
GEO. PAVLIDES & ARAOUZOS LTD,
Τηλ: +35722818087

Latvija
Pfizer Luxembourg SARL
Filiāle Latvijā
Tel: +371 670 35 775

Lietuva
Pfizer Luxembourg SARL
filialas Lietuvoje
Tel. +3705 2514000

Tel: +31 (0)10 406 43 01

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: + 351 214 235 500

România
Pfizer România S.R.L
Tel: +40 (0)21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: + 386 (0)152 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421-2-3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358(0)9 43 00 40

Sverige
Pfizer AB
Tel: +46 (0)8 5505 2000

United Kingdom
Pfizer Limited
Tel: +44 (0)1304 616161

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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The following information is intended for medical or healthcare professionals only and applies only to the single vial ECALTA 100 mg powder for concentrate for solution for infusion presentation:

The contents of the vial must be reconstituted with water for injections 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 ECALTA 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.

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 discoloration is identified.

The reconstituted solution may be stored up to 25°C for up to 24 hours prior to further dilution.

Dilution and infusion
Aseptically transfer the contents of the reconstituted vial(s) 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 obtaining an anidulafungin concentration of 0.77 mg/ml. The table below provides the volumes required for each dose.

Dilution requirements for ECALTA administration

Dose	**Number of vials of powder**	**Total reconstituted volume**	**Infusion volume [A]**	**Total infusion volume [B]**	**Rate of infusion**	**Minimum duration of infusion**
100 mg	1	30 ml	100 ml	130 ml	1.4 ml/ min	90 min
200 mg	2	60 ml	200 ml	260 ml	1.4 ml/ min	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 (equivalent to 1.4 ml/minute when reconstituted and diluted per instructions).

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 discolouration are identified, discard the solution.

For single use only. Waste materials should be disposed of in accordance with local requirements.