ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ECALTA 100 mg powder and solvent 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 0.36 mg/ml anidulafungin.

Excipients: Fructose 102.5 mg per vial
Ethanol 6 g per vial

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.
Powder: White to off-white lyophilised solid.
Solvent: Clear colourless solution.
The reconstituted solution has a pH of 4.0 to 6.0.

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 section 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.

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.

ECALTA should be reconstituted with the solvent to a concentration of 3.33 mg/ml and subsequently diluted to a concentration of 0.36 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 3.0 ml/minute). Infusion associated reactions are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute.

ECALTA should not be administered as a bolus injection.

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).

Duration of treatment

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

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).

Children and adolescents

ECALTA is not recommended for use in children below 18 due to insufficient data on safety and efficacy (see section 5.2).

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

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. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported. 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.

Infusion-related reactions

Exacerbation of infusion-related reactions by coadministration 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.

Alcohol content

This medicinal product contains 24 vol% ethanol (alcohol); this is equivalent to 6 g ethanol in the 100 mg maintenance dose (administered over a 1.5-hour period), and 12 g ethanol in the 200 mg loading dose (administered over a 3-hour period). Ethanol could be harmful for those suffering from alcoholism. This should be taken into account in pregnant or breast-feeding women, children, and in high-risk groups such as those with liver disease or epilepsy.
The amount of alcohol in this medicinal product may alter the effects of other medicines.
The amount of alcohol in this medicinal product may impair the ability to drive or use machines.

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 Pregnancy and lactation

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.

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.

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.
The amount of alcohol in this medicinal product may impair the ability to drive or use machines.

4.8 Undesirable effects

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 hypokalemia (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%).

In the 100 mg ICC database (N = 204), the drug-related adverse reactions (MedDRA) listed below were reported with frequencies corresponding to Common (≥1/100 to <1/10) or Uncommon (≥1/1,000

to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Common: Coagulopathy

Nervous system disorders

Common: Convulsion, headache

Gastrointestinal disorders

Common: Diarrhoea, vomiting, nausea
Uncommon: Abdominal pain upper

Renal and urinary disorders

Common: Blood creatinine increased

Skin and subcutaneous tissue disorders

Common: Rash, pruritus
Uncommon: Urticaria

Metabolism and nutrition disorders

Common: Hypokalaemia
Uncommon: Hyperglycaemia

Vascular disorders

Common: Flushing
Uncommon: Hypertension, hot flush

General disorders and administration site conditions

Uncommon: Infusion site pain

Hepatobiliary disorders

Common: Alanine aminotransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased
Uncommon: Cholestasis

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

General properties
Pharmacotherapeutic group: Other antimycotics for systemic use, ATC code: JO2AX06

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 and M38. *Candida* isolates with reduced susceptibility to anidulafungin have not been isolated from treated patients. Among a number of isolates with elevated echinocandin MICs isolated from patients treated with other echinocandins, only two *Candida* isolates were reported to also have elevated anidulafungin MICs, suggesting the lack of complete cross resistance among echinocandins.

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.*

Information from clinical studies

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 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.

Crossing of the blood-brain barrier by anidulafungin was limited in healthy rats; however, in rabbits with disseminated candidiasis, anidulafungin has been shown to cross the blood-brain barrier and reduce fungal burden in the brain.

Rats were dosed with anidulafungin at three dose levels and anesthetised 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

Powder*:*
Fructose
Mannitol
Polysorbate 80
Tartaric acid
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

Solvent**:**
Ethanol anhydrous
Water for injections

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

Powder and solvent: 3 years

Reconstituted solution:
The reconstituted solution should be further diluted within an hour. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 3 hours at 25ºC and for 2 hours at 5°C.

Infusion solution:
Chemical and physical in-use stability of the infusion 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 times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Powder and solvent:
Do not store above 25ºC.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:
30 ml Type 1 glass vial with an elastomeric stopper and aluminium seal with flip-off cap.

Solvent:
30 ml of 20 % (w/w) ethanol anhydrous in water for injections in a Type 1 glass vial with an elastomeric stopper and aluminium seal with flip-off cap.

ECALTA will be available as a box containing 1 vial of 100 mg powder and 1 vial of 30 ml solvent.

6.6 Special precautions for disposal and other handling

ECALTA must be reconstituted with the solvent (20% (w/w) ethanol anhydrous in 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 the solvent (20% (w/w) ethanol anhydrous in water for injections) to provide a concentration of 3.33 mg/ml. The reconstitution time can be up to 5 minutes. The reconstituted solution should be clear and free from visible particulates. After subsequent dilution, the solution is to be discarded if particulate matter or discoloration is identified.

The reconstituted solution must be further diluted within an hour and administered within 24 hours.

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 0.36 mg/ml. The table below provides the volumes required for each dose.

Dilution requirements for ECALTA administration

Dose	Number of boxes	Total reconstituted volume	Infusion volume [A]	Total infusion volume	Infusion solution concentration	Rate of infusion
100 mg	1	30 ml (1 box)	250 ml	280 ml	0.36 mg/ml	3.0 ml/min
200 mg	2	60 ml (2 boxes)	500 ml	560 ml	0.36 mg/ml	3.0 ml/min

[A] Either 9 mg/ml (0.9%) sodium chloride for infusion or 50 mg/ml (5%) glucose for infusion.

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.

7 MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/416/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 September 2007

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Belgium N.V.
Rijksweg 12
BE-2870 Puurs
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 (9 February 2009 and included in variation EMEA/H/C/788/II/10) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.2 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the 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 EMEA

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 and solvent 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 0.36 mg/ml anidulafungin.

3. LIST OF EXCIPIENTS

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

Solvent for concentrate for solution for infusion:
Contains ethanol anhydrous and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of 100 mg powder
1 vial of 30 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute and dilute before use – read the package leaflet before use.
For intravenous use only.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MONTH – YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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/1/07/416/001

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Solvent Vial label

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

Solvent for concentrate for solution for infusion for ECALTA
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

30 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ECALTA 100 mg powder and solvent for concentrate for solution for infusion
Anidulafungin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ECALTA IS AND WHAT IT IS USED FOR

ECALTA is prescribed to treat a type of fungal infection of the blood called candidaemia. 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 anidulafungin, fungal cells have incomplete or defective cell walls, making them fragile or unable to grow.

2. WHAT YOU SHOULD KNOW BEFORE YOU ARE TREATED WITH ECALTA

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

Take special care with ECALTA
- if you develop liver problems during your treatment. If this happens, your doctor may decide to monitor your liver function more closely.
- if you are given anaesthetics during your treatment with ECALTA.

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

Taking other medicines
There are no known interactions with other medicines likely to be given at the same time as ECALTA (i.e., rifampicin, ciclosporin, tacrolimus, voriconazole and amphotericin B).
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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 chilbearing 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.

Driving and using machines
No studies on the effect on the ability to drive and use machines have been performed.

Important information about some of the ingredients of ECALTA
This medicinal product 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.

This medicinal product contains 24 vol% ethanol (alcohol), i.e. up to 6 g per dose consumed over a 1.5 –hour period (12 g loading dose consumed over a 3-hour period); this is equivalent to 144 ml beer (288 ml beer for the loading dose) or 60 ml wine (120 ml wine for the loading dose). Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children, and in high-risk groups such as those with liver disease or epilepsy.
The amount of alcohol in this medicinal product may alter the effects of other medicines.
The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

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.
Do not take a double dose to make up for a forgotten dose.

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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ECALTA can cause side effects, although not everybody gets them.

Common side effects (likely to occur in fewer than 1 in 10 patients):
- 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 (likely to occur in fewer than 1 in 100 patients):
- 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

If any of the side effects you experience are severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ECALTA

Keep out of the reach and sight of children.
Do not use ECALTA after the expiry date which is stated on the label. The expiry data refers to the last day of that month.
Do not store ECALTA above 25ºC.
The reconstituted solution should not be stored above 25ºC. Do not freeze.
The infusion solution should not be stored above 25ºC. Do not refrigerate or freeze.
Medicines should not be disposed of via wastewater or household waste.

6. FURTHER INFORMATION

What ECALTA contains

- The active substance is anidulafungin. Each vial with powder contains 100 mg anidulafungin.

- The other ingredients are

Powder: fructose, mannitol, polysorbate 80, tartaric acid, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment)

Solvent: ethanol anhydrous, water for injections

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 and 1 vial of 30 ml solvent.
The powder for concentrate for solution for infusion is white to off-white. The solvent is a clear colourless solution.

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 medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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

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

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The following information is intended for medical or healthcare professionals only:
ECALTA must be reconstituted with the solvent (20% (w/w) ethanol anhydrous in 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 the solvent (20% (w/w) ethanol anhydrous in water for injections) to provide a concentration of 3.33 mg/ml. The reconstitution time can be up to 5 minutes. The reconstituted solution should be clear and free from visible particulates. After subsequent dilution, the solution is to be discarded if particulate matter or discoloration is identified.

The reconstituted solution must be further diluted within an hour and administered within 24 hours.

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 0.36 mg/ml. The table below provides the volumes required for each dose.

Dilution requirements for ECALTA administration

Dose	Number of boxes	Total reconstituted volume	Infusion volume [A]	Total infusion volume	Infusion solution concentration	Rate of infusion
100 mg	1	30 ml (1 box)	250 ml	280 ml	0.36 mg/ml	3.0 ml/min
200 mg	2	60 ml (2 boxes)	500 ml	560 ml	0.36 mg/ml	3.0 ml/min

[A] Either 9 mg/ml (0.9%) sodium chloride for infusion or 50 mg/ml (5%) glucose for infusion.

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.