HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

5 March 2008

ECALTA 100 mg, powder and solvent for concentrate for solution for infusion
Box containing 1 30 mL glass bottle (CIP: 382 047-1)

Applicant: PFIZER

anidulafungin

ATC Code: JO2AX06

List I
Medicinal product for hospital prescription only

Marketing Authorisation (MA) date: 20 September 2007 (centralised procedure)

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

anidulafungin

1.2. Indication

“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 of the SPC).”

1.3. Dose

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 of the SPC.

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 of the SPC).

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 status, or geriatric status (see section 5.2 of the SPC).

Children and adolescents

ECALTA is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy (see section 5.2 of the SPC).”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J - General anti-infectives for systemic use
J02 - Antimycotics for systemic use
J02AX - Other antimycotics for systemic use
JO2AX06 - anidulafungin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Other echinocandins indicated for the treatment of invasive candidiasis in adults.

- CANCIDAS (caspofungin), powder for solution for infusion 50 mg or 70 mg

2.3. Medicines with a similar therapeutic aim

Antifungals for systemic use, indicated for infection with *Candida* spp.

IV forms:

- FUNGIZONE (amphotericin B), powder for solution for injection 50 mg
- ABELCET (amphotericin B lipid complex) concentrate for suspension for infusion 5 mg/mL
- AMBISOME (liposomal amphotericin B), powder for liposomal suspension for infusion 50 mg

Oral and IV forms

- ANCOTIL (flucytosine), 500 mg tablet and 1% solution for infusion
- TRIFLUCAN (fluconazole) 100 mg and 200 mg capsules, powder for oral suspension 200 mg/5mL, solution for infusion 2 mg/mL, and generics
- VFEND (voriconazole), 50 mg and 200 mg tablets, powder for oral suspension 40 mg/mL, powder for solution for infusion 200 mg

Oral form

- NIZORAL (ketoconazole), 200 mg tablet

3 ANALYSIS OF AVAILABLE DATA

Three studies were included in the dossier:

- Two phase III studies: One comparative study versus fluconazole (VER002-9)[1] and one non-comparative study (VER002-9B)
- One phase II non-comparative study (VER002-6)

3.1. Efficacy

The clinical dossier is primarily based on a controlled phase III study (VER002-09), the primary objective of which was to compare the efficacy of anidulafungin and fluconazole in the treatment of patients with candidaemia and other forms of invasive candidiasis

- **Methodology**

Population

Patients (aged 16 years and over) had a diagnosis of candidaemia or another form of invasive candidiasis. The diagnosis was based on a positive blood culture of *Candida* during the 96 hours prior to randomisation or a positive culture from at least one other normally sterile site, and clinical evidence of infection (temperature > 38°C, hypothermia, systolic blood pressure < 100 mmHg or a fall of more than 30 mmHg from baseline, signs or symptoms of candidaemia/invasive candidiasis, signs on X-ray suggestive of invasive candidiasis).

[1] Reboli AC *et al*. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med. 2007 Jun 14;356(24):2472-82.

Exclusion criteria:

- patients with *Candida* endocarditis, osteomyelitis or meningitis, and those with *C. krusei* infection.
- patients who had been treated for more than 48 hours with a systemic antifungal to treat *Candida* infection
- patients in whom systemic antifungal treatment for *Candida* infection had failed
- patients who had received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrolment.

Treatments

Eligible patients (n=261) were randomised (1:1 ratio), after stratification by APACHE II score at baseline (≤20 and >20) and absence or presence of neutropenia (neutrophils ≤500 and >500 cells/m^3), and received either:

- Anidulafungin IV (n=132) administered as a loading dose of 200 mg/day on the first day followed by a maintenance dose of 100 mg/day
- or fluconazole IV (n=129) administered as a loading dose of 800 mg/day on the first day followed by a maintenance dose of 400 mg/day.

Patients had to receive treatment for a minimum of 14 days from the time of the last negative culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total treatment duration was not to exceed 42 days.

Patients in both groups could switch to oral fluconazole after a minimum of 10 days of intravenous treatment, if they could tolerate oral treatment, if they had been afebrile for at least 24 hours and if the last blood culture was negative for Candida species.

Endpoints

The primary endpoint was success rate (clinical and microbiological success rate) at the end of IV treatment in the modified intent-to-treat population (mITT)[2].

Clinical success was defined as cure (resolution of signs and symptoms of *Candida* infection, no use of other systemic antifungals or additional oral fluconazole) or improvement (incomplete resolution of signs and symptoms of *Candida* infection, and no additional systemic antifungal treatment or additional oral fluconazole required). Microbiological success was defined as documented or presumed eradication of *Candida.*

A patient was categorized as a failure if there was either a clinical or microbiological failure. A patient was categorized as indeterminate if there was a clinical and/or microbiological response of indeterminate.

Statistical methods

This study was designed to demonstrate non-inferiority of anidulafungin to fluconazole, and if possible superiority, if non-inferiority were demonstrated.

Anidulafungin would be considered non-inferior to fluconazole if the lower bound of the 95% CI (calculated around the difference between the global response rates of the 2 treatment groups) at the end of IV treatment exceeded -20%. Superiority would be established if the lower limit of the 95% confidence interval were positive.

- **Results**

256 patients, aged between 16 and 91, were randomised and received at least one dose of treatment.

At baseline, patient demographics and medical characteristics were similar in both treatment groups. Mean age was 57 years in the anidulafungin group and 59 in the fluconazole group.

The majority of patients (around 80%) had an APACHE II score ≤ 20 (mean score: 15 ± 7.7 *vs* 14.4 ± 6.8) and very few patients were neutropenic (2% *vs* 3%). The main underlying pathologies were: diabetes and metabolic disease (35% *vs* 25%), renal insufficiency (37% *vs*

[2] mITT: All patients who received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site within 96 hours before entry into the study.

36%), septic shock (46% *vs* 42%), neoplasia (22% *vs* 23%). 6% and 4% of patients had recently undergone organ or haematopoietic stem cell transplantation.
The most frequently isolated pathogenic microorganisms were: *C. albicans* (63.8% in the anidulafungin group *vs* 59.3 % in the fluconazole group), *C. glabrata* (15.7 % *vs* 25.4 %), *C. parapsilosis* (10.2 % *vs* 13.6 %) and *C. tropicalis* (11.8 % *vs* 9.3 %). Very few isolates were not sensitive to fluconazole in vitro (10/242).
In the two treatment groups, fluconazole was the most frequently administered empirical treatment in the 48 hours prior to inclusion (62.6% *vs* 68.8%).
Median treatment duration was 15 days in the anidulafungin group and 14 days in the fluconazole group. The majority of patients (74% *vs* 71.2%) did not switch to oral fluconazole treatment.

Table 1: Global success rates in study VER002-9

		Anidulafungin n/N (%)	**Fluconazole n/N (%)**	**Difference % (95% CI)**
End of IV treatment	P-P population	90/103 (87.4)	68/91 (74.7)	12.65 (1.66 ; 23.65)
	mITT population	96/127 (75.6)	71/118 (60.2)	15.42 (3.85 ; 26.99)
End of treatment (IV + oral)	P-P population	88/103 (85.4)	64/87 (73.6)	11.87 (0.37 ; 23.37)
	mITT population	94 /127 (74.0)	67/118 (56.8)	17.24 (5.49 ; 28.99)
2-week follow-up	P-P population	71/ 88 (80.7)	51/ 76 (67.1)	13.58 (0.17 ; 26.98)
	mITT population	82 /127 (64.6)	58 / 118 (49.2)	15.41 (3.14 ; 27.68)
6-week follow-up	P-P population	59/79 (74.7)	43/ 69 (62.3)	12.36 (-2.56 ; 27.29)
	mITT population	71/ 127 (55.9)	52 /118 (44.1)	11.84 (- 0.60 ; 24.28)

mITT population (modified Intent-to-treat population): All patients who received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site within 96 hours before entry into the study.
P-P population (Per-Protocol population): Patients in the mITT population with no protocol violations

On the primary endpoint, anidulafungin was superior to fluconazole in terms of global response at the end of IV treatment in the mITT population. Global success was 75.6% in the anidulafungin group, *vs* 60.2% in the fluconazole group (difference 15.42%; 95% CI [3.85; 26.99]).

An additional analysis was carried out following a CHMP request, with a revised definition of success (clinical success was defined as cure; improvement was considered to be a failure). Success rates observed (67.7 % *vs* 57.6 %; 95% CI of the difference [-1.98; 22.16]) confirm that anidulafungin is non-inferior to fluconazole.

At the end of the 6-week post-treatment follow-up period, anidulafungin was non-inferior to fluconazole (74.7 % *vs* 62.3%; 95% CI of the difference [-2.56; 27.29]).

Microbiological success rates at the end of IV treatment were greater in the anidulafungin group than in the fluconazole group for all isolated *Candida* spp. (88% *vs* 76%; p=0.02) and for *Candida albicans* (95% *vs* 81%; p=0.01).
For infection involving C*andida glabrata*, *Candida tropicalis, Candida parapsilosis* and other *Candida* species, no significant difference was observed between the two treatment groups.

Sub-group analysis carried out using APACHE II scores revealed that success rates for patients with an APACHE II score of ≤ 20 were greater in the anidulafungin group (81.2%) than in the fluconazole group (61.2%). Conversely, in patients with an APACHE II score of > 20, success rates were lower, and were similar in the two treatment groups (53.8% *vs* 55%).

All-cause mortality was 22.8% (29/127) in the anidulafungin group *versus* 31.4% (37/118) in the fluconazole group, though the difference was not statistically significant.

Supportive study

Study VER002-9B is a non-comparative additional study to study VER002-9 (N=33 patients). Unlike VER002-09, this study included the following patient categories:

- patients who had received prophylactic administration of fluconazole, itraconazole, or voriconazole for at least one week within 30 days prior to enrolment
- patients who had received terfenadine or cisapride treatment
- patients with *Candida krusei* infection
- patients with known hypersensitivity to azoles.

Clinical and microbiological success rates observed in this study confirm the results observed in the VER002-9 pivotal study. However, these data are currently limited and do not enable conclusions to be drawn concerning these points of interest.

3.2. Safety

Three studies (one comparative study versus fluconazole, two non-comparative studies) were done to evaluate the efficacy of anidulafungin in patients with candidaemia and in a limited number of patients with deep tissue candidiasis.
In total, 204 patients received the recommended daily dose of 100 mg, and the mean duration of intravenous treatment for these patients was 13.5 days (range: 1-38 days). Duration of anidulafungin treatment was greater than or equal to 14 days in 119 patients. Overall, adverse events were mild to moderate and in rare cases required treatment to be stopped.
Infusion-linked reactions have been described for anidulafungin: flushing (2.3%), pruritis (2.3%), skin eruption (1.5%) and urticaria (0.8%). Other treatment-linked adverse effects that occurred in ≥ 1% of patients were: hypokalaemia (3.1%), diarrhoea (3.1%), increased ALT (2.3%), increased liver enzymes (1.5%), blood alkaline phosphatase (1.5%) and blood bilirubin (1.5%).

Overall, the available data show that anidulafungin has a similar safety profile to fluconazole in the treatment of invasive candidiasis.

Anidulafungin is marketed on condition that a risk management plan be put in place in order to monitor, in particular, significant risks that have been identified (injection-linked reactions, hepatobiliary events), potentially significant risks (convulsions, injection-linked reactions that are made worse by anaesthesia, QT prolongation/torsade de pointed), the development of resistance and in order to collect data on populations in which experience is currently limited: the paediatric population, neutropenic patients, pregnant and breastfeeding women, the elderly.

3.3. Conclusion

Clinical efficacy of anidulafungin has been documented primarily via a controlled phase III study (VER002-9), the objective of which was to demonstrate non-inferiority, and superiority if possible, of anidulafungin (200 mg/day followed by 100 mg/day) in comparison with fluconazole (800 mg/day followed by 400 mg/day) in the treatment of candidaemia and/or other forms of invasive candidiasis. Patients in whom systemic antifungal treatment for *Candida* infection had failed, patients who had been treated for more than 48 hours with systemic antifungal agent because of *Candida* infection, patients with *Candida* endocarditis, osteomyelitis or meningitis and those with *C. krusei* infection (fluconazole-resistant) could not be included in the study.

A total of 256 patients were included in this study of which 245 were in the modified ITT population[3] (127 in the anidulafungin group and 118 in the fluconazole group). Median treatment duration (IV + switch to oral fluconazole) was 15 days in the anidulafungin group and 14 days in the fluconazole group, with the majority of patients (74% *versus* 71.2%) not switching to oral fluconazole treatment.

[3] mITT: All patients who received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site within 96 hours before entry into the study.

Rates of clinical[4] and microbiological success (documented or presumed eradication) at the end of IV treatment, which was the primary endpoint, were greater in the anidulafungin group than in the fluconazole group (75.6% *vs* 60.2%; difference 15.42%, 95% CI [3.95; 26.99]).

For the secondary endpoints (in particular success rates after 6 weeks of follow-up) and on post-hoc analysis, the observed therapeutic response confirms that anidulafungin is non-inferior to fluconazole. Safety seems good, and is comparable with that of fluconazole.

The Transparency Committee's conclusion concerning this study is that, although it demonstrates that anidulafungin is non-inferior to fluconazole, the quality of evidence to support superiority is suboptimal. In addition, the clinical relevance of the results of this study are debatable. The chosen comparator (fluconazole) has a narrower activity spectrum (C. krusei is resistant and C. glabrata has dose-dependent sensitivity) than echinocandins, amphotericin B and voriconazole, which explains why some patients infected with non-albicans Candida (C. krusei) were not included in the study. The clinical efficacy of anidulafungin has therefore mostly been evaluated in non-neutropenic patients with *C. albicans* infections (63.8%) and in a small number of patients with non-albicans infections, primarily *C. glabrata, C. parapsilosis* and *C. tropicalis*. The number of patients with an APACHE II score of > 20 was limited, which prevents conclusions being drawn as to efficacy in patients with worse prognoses.

The available data do not, therefore, provide a means of precisely delineating the role of this product in comparison with medicinal products recommended in current management strategies, particularly in patients with severe or fluconazole-resistant infection.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Invasive candidiasis is a serious infection, because of the risk of progression to septic shock and the high mortality rates associated with it.

This product is intended to provide curative treatment.

The efficacy/adverse reactions ratio for this medicinal product is high.

Public health benefit

Invasive candidiasis in a non-neutropenic patient is a serious and life-threatening clinical situation, which represents a slight public health burden, given the small numbers of patients affected.

Improvement to treatment for invasive candidiasis, particularly involving fluconazole-resistant strains and some very severe forms, is a significant clinical need but does not represent a high-priority public health need.

As it has not been demonstrated that ECALTA is effective in patients with fluconazole-resistant candidaemia or deep tissue candidiasis (endocarditis, osteomyelitis, meningitis), it is not certain that results of this trial can be transposed to these patients. The profile of patients who are expected to need a new antifungal does not correspond to the patients in this trial.

There is therefore no expected impact in terms of morbidity and mortality in this target population.

As a result, this product is not expected to benefit public health.

The actual clinical benefit of this product is substantial.

[4] Clinical success: Resolution of signs and symptoms of *Candida spp.* infection, no additional systemic antifungal treatment or oral fluconazole required; improvement: incomplete resolution of signs and symptoms of *Candida spp.* infection, no additional systemic antifungal treatment or oral fluconazole required

4.2. Improvement in actual benefit

Given the modest observed difference in effect in comparison with fluconazole, the suboptimal quality of evidence demonstrating superiority and the doubts concerning how these results would transpose to actual clinical practice, the Committee considers that ECALTA presents no improvement in actual benefit (IAB V) in comparison to fluconazole-based products with a sufficient quality of evidence.

It is a supplementary therapy, and its role in therapeutic use needs to be clarified.

4.3. Therapeutic use

Current management of candidaemia in adults was defined at the consensus conference "Management of invasive candidiasis and aspergillosis in adults" in France in May 2004.

- **Therapeutic strategies for systemic candidiasis**

The consensus conference in 2004 recommended use of amphotericin B for treatment of systemic candidiasis in the absence of renal insufficiency (blood creatinine < 1.5 times the upper limit of normal), or fluconazole unless the patient is neutropenic or has received fluconazole previously. In patients with renal insufficiency who have previously received fluconazole or who are receiving at least 2 nephrotoxic treatments; caspofungin or liposomal amphotericin B are recommended. If the strain is sensitive to fluconazole, switching to fluconazole treatment is recommended, and if the strain is resistant or has dose-dependent sensitivity to fluconazole, treatment with amphotericin B, voriconazole, caspofungin or liposomal amphotericin B is prescribed.

In cases of candidaemia, the duration of treatment is 2 weeks following the last positive blood culture. Removal of any intravascular catheters is recommended.

Treatment strategies[5] according to genes and species after isolation of yeast and before and after species identification are shown in the decision trees below.

[5] Consensus conference involving SFAR, SPILF, SRLF: Prise en charge des aspergilloses et candidoses invasives de l'adulte [Management of invasive aspergillosis and candidiasis in adults]. Elsevier SAS. 2004.

Figure 1: Treatment strategy after yeast is isolated and before species is identified

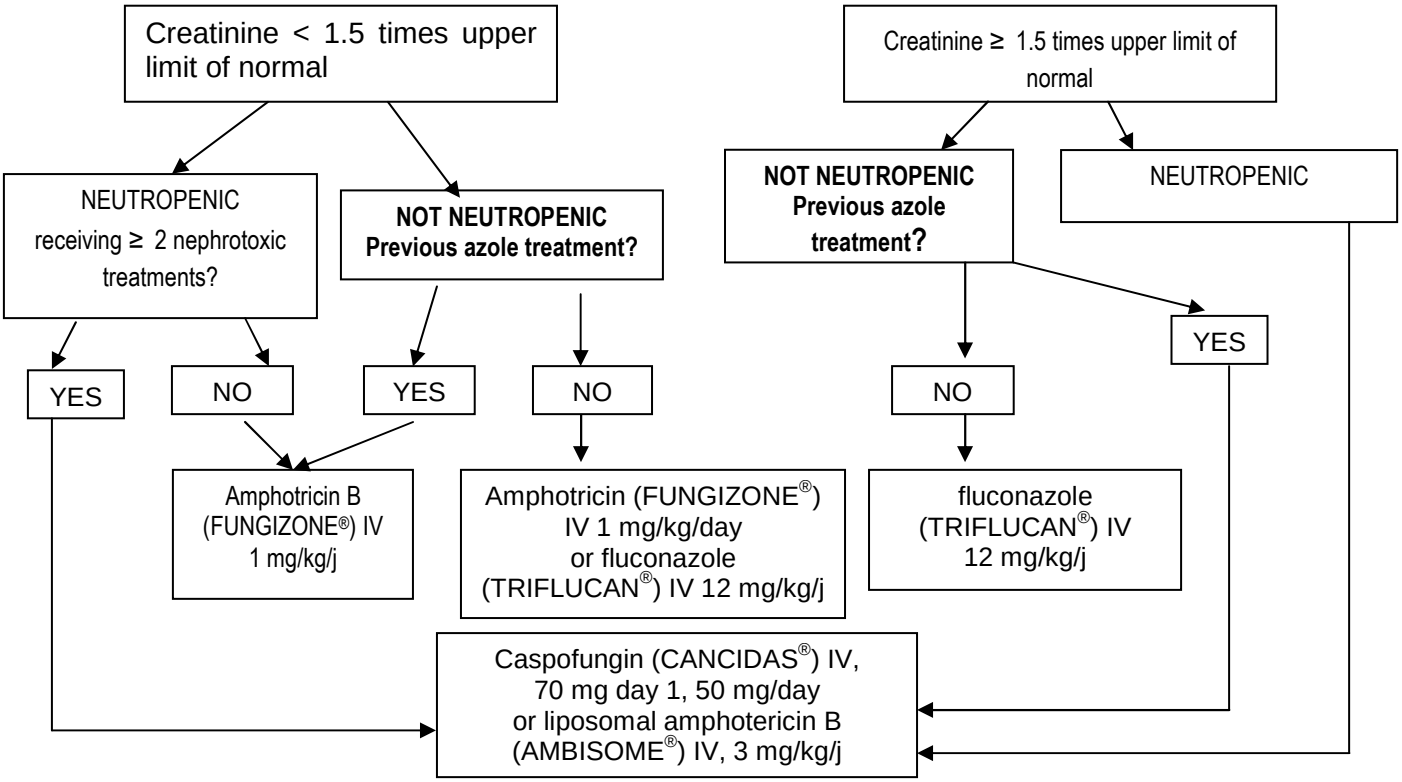
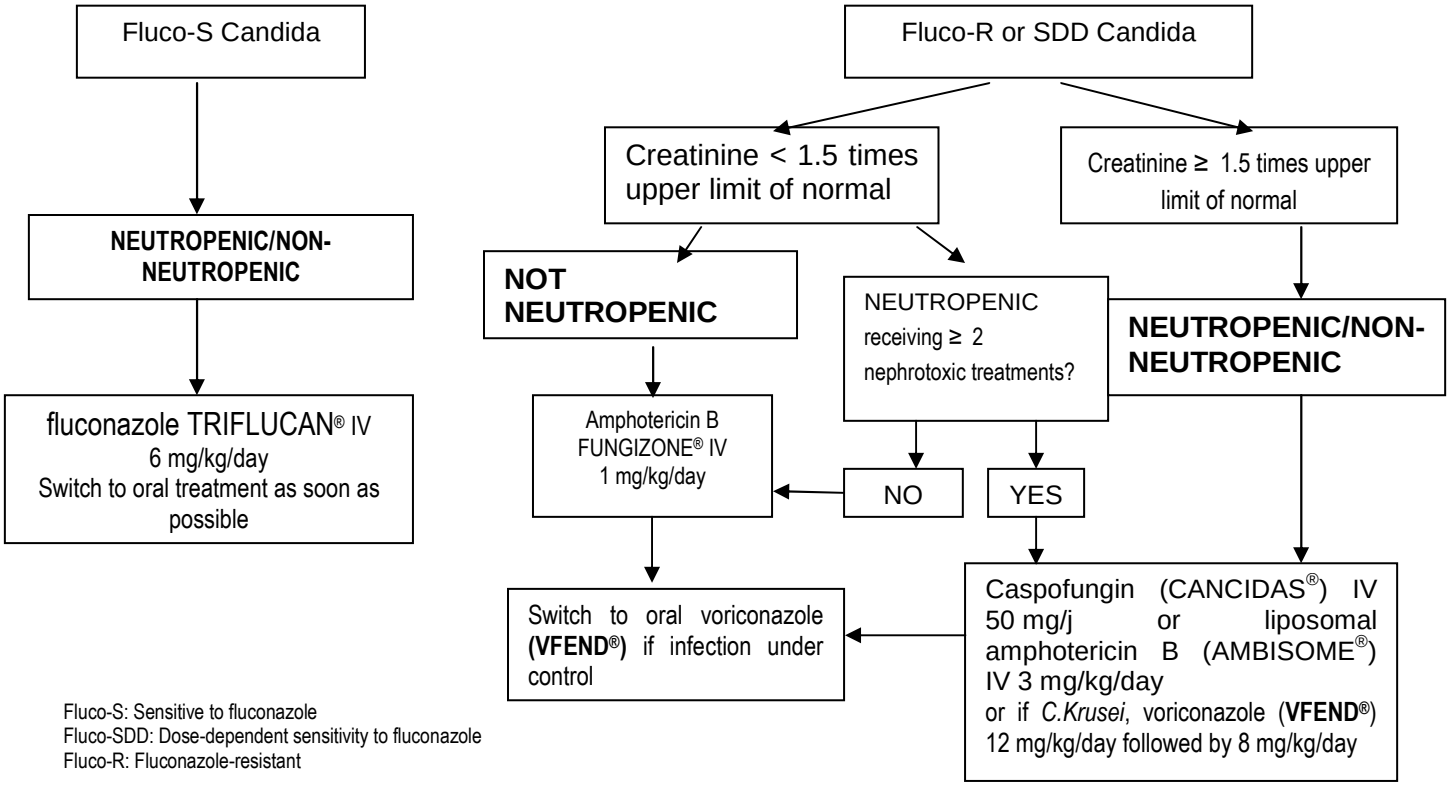


Figure 2: Treatment strategy after identification of *Candida* species



Fluco-S: Sensitive to fluconazole
Fluco-SDD: Dose-dependent sensitivity to fluconazole
Fluco-R: Fluconazole-resistant

- **Role of anidulafungin (ECALTA) in management of invasive candidiasis in adults**

ECALTA can be considered to have the same indications as caspofungin. However, unlike caspofungin, ECALTA does not have MA for use in neutropenic patients. Its in vitro activity spectrum means that it is expected to have in vivo activity against *Candida non albicans.* However, clinical data on efficacy are limited, for fluconazole-resistant *Candida albicans or* non-albicans *Candida* infections (54 patients in the VER002-9 study).

4.4. Target Population

The target population for ECALTA is the group of non-neutropenic adult patients with invasive candidiasis.

The incidence of candidaemia can be evaluated at between 0.20 and 0.29 cases per 1000 hospital admissions[6][7]. According to Richet's study[5] on the incidence of candidaemia, the proportion of patients who are not neutropenic can be estimated at 77%.

The number of stays greater than 24 hours in medical, surgical and obstetric wards in 2004, in private and public hospitals in France, was 9,862,000[8].

Using these data, it is possible to estimate the number of cases of candidaemia at between 1973 and 2860/year.

The target population, corresponding to non-neutropenic patients requiring treatment for candidaemia, can therefore be estimated at between **1500** and **2200**/year.

6 Tortorano A.M, Peman J, Bernhardt H, Kllinspor L, Kibbler C, Faure O, Biraghi E, Canton E, Zimmermann K, Seaton S, Grillot R. The ECMM Working Group on Candidaemia, Epidemiology of candidaemia in Europe: results of 28-Month European Confederation of Medical Mycology (ECMM) Hospital-Based Surveillance Study, Eur J Microbiol Infect Dis, 2004, 23: 317-22

7 Richet H, Roux P, Des Champs C, Esnault Y. Candidemia in French Hospitals: incidence rates and characteristics, Clin Microbiol Infect, 2002, 8: 405-412

8 DREES.L'activité des établissements de santé en 2004 en hospitalisation complète et partielle [Activity of healthcare establishments in 2004: full and partial admissions]. No. 456, December 2005.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage of the Marketing Authorisation.