HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

8 September 2010

ECALTA 100 mg, powder and solvent for concentrate for solution for infusion
Glass vials: - powder: 100 mg powder, - solvent: 30 ml
B/1 vial of powder + B/1 vial of solvent (CIP code: 382 047-1)
B/1 vial of 30 ml (powder for concentrate for solution for infusion) (CIP code: 395 983-2)

Applicant: PFIZER

anidulafungin
ATC code: JO2AX06

List I – Medicine for hospital prescription only.

Date of Marketing Authorisation (centralised European procedure): 20 September 2007

Reason for request: Re-assessment of IAB.

Medical, Economic, and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

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. Dosage

"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.

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.

Children and adolescents
ECALTA is not recommended for use in children below 18 due to insufficient data on tolerance and efficacy."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification

J : 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 in the treatment of invasive candidiasis in non-neutropenic adults (see appendix):

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

- MYCAMINE (micafungin), 50 mg or 100 mg powder for solution for infusion

2.3. Medicines with a similar therapeutic aim

Antifungals for systemic use that are indicated in infections with *Candida spp*:

IV forms:

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

Oral and IV forms:

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

Summary of the indications for comparator treatments:

Medicinal product	Indications
Fluconazole (TRIFLUCAN)	Systemic candidiasis including disseminated and deep candidiasis (candidaemia, peritonitis), oesophageal candidiasis and urinary candidiasis. *Candida albicans* accounts for most of the species isolated in clinical studies. Efficacy has not been established in infections due to other *Candida* species, particularly *Candida glabrata* and *Candida krusei* (a species which is usually resistant).
Flucytosine (in combination) (ANCOTIL)	Severe systemic mycoses with sensitive microorganisms, as an alternative to or when switching to parenteral administration in particular: candidiasis, cryptococcosis, chromomycosis and certain forms of aspergillosis. Combination with another antifungal: It is essential to use flucytosine in combination so as to avoid, as far as possible, the selection of resistant mutants, particularly in the treatment of candidiasis and cryptococcosis. Combination with amphotericin B is often synergistic and never antagonistic
Caspofungin (CANCIDAS)	Treatment of invasive candidiasis in adult patients
Micafungin (MYCAMINE)	Treatment of invasive candidiasis. The decision to use MYCAMINE must take account of the potential risk of developing liver tumours. Thus, MYCAMINE should be used only if the administration of other antifungals is not appropriate.
Voriconazole (VFEND)	Treatment of serious invasive infections with Candida (including C. krusei) resistant to fluconazole. Treatment of candidaemia in non-neutropenic patients VFEND should be administered mainly to patients with potentially life-threatening progressive infections
Amphotericin B (AMBISOME, ABELCET)	Treatment of systemic and/or deep aspergillus and candida mycoses
Amphotericin B (FUNGIZONE)	Systemic mycoses with sensitive microorganisms

Medicinal products	Population for the indication invasive candidiasis						
	Non-neutropenic patients				Neutropenic patients	Adults	Children
	Fluco-sensitive microorganism		Fluco-resistant microorganism				
	Non-severe forms	Severe forms	Non-severe forms	Severe forms			
Anidulafungin	X		X			X	
Fluconazole	X	X			X	X	X
Flucytosine (in combination)		X		X	X	X	X
Caspofungin	X	X	X	X	X	X	X
Micafungin	X	X	X	X	X	X	X
Voriconazole	X	X	X	X	X	X	X
Amphotericin B	X	X	X	X	X	X	X

3 ANALYSIS OF AVAILABLE DATA

3.1. Summary of the conclusions of the previous opinion

"The clinical efficacy documentation for anidulafungin is based mainly on a phase III controlled study (VER002-9[1]) the objective of which was to demonstrate the non-inferiority and possibly the superiority of anidulafungin (200 mg/day followed by 100mg/day) compared with fluconazole (800 mg/day followed by 400 mg/day) in the treatment of candidaemia and/or other forms of invasive candidiasis. This study excluded patients in whom systemic antifungal treatment for *Candida* infection had failed, patients who had been treated for more than 48 hours with a systemic antifungal for *Candida* infection, patients with endocarditis, osteomyelitis or *Candida* meningitis and those infected with *C. krusei (resistant to fluconazole)*.

A total of 256 patients were included in this study, 245 of them in the modified intention to treat population[2] (127 in the anidulafungin group and 118 in the fluconazole group). The median duration of treatment (IV + oral fluconazole) was 15 days in the anidulafungin group and 14 in the fluconazole group; most of the patients (74% *versus* 71.2%) did not have the course of oral fluconazole.

The clinical[3] and microbiological success rate (eradication documented or presumed) at the end of the IV treatment, the primary endpoint) was higher in the anidulafungin group than in the fluconazole group (75.6% vs 60.2%; difference 15.42%, 95% CI [3.85; 26.99]).

On the basis of the secondary endpoints (in particular the success rate after 6 weeks' follow-up) and the post-hoc analyses, the response to treatment observed confirms the non-inferiority of anidulafungin compared with fluconazole. Tolerance seems to be good, comparable to that of fluconazole.

The Transparency Committee's conclusion on this study is that, although it demonstrates the non-inferiority of anidulafungin compared with fluconazole, its level of evidence in terms of superiority is not optimal. Moreover, the clinical relevance of the results of this study is debatable. In fact, the comparator selected (fluconazole) has a narrower spectrum of activity (*C. krusei* is resistant and *C. glabrata* has dose-dependent sensitivity) than echinocandins, amphotericin B and voriconazole, which explains why some patients infected with candida non-albicans (*C. krusei*) were not included in the study. The clinical efficacy of anidulafungin was therefore evaluated mainly in non-neutropenic patients with *C. albicans* infections *(63.8%)* and in a small number of patients infected with non-*albicans* strains, mainly *C. glabrata, C. parapsilosis* and *C. tropicalis*. The number of patients with an APACHE II score of > 20 was limited, which means that no conclusions can be drawn about efficacy in these patients who have a more serious prognosis.

The data available therefore do not permit any precise ranking of this medicinal product in relation to the medicines currently recommended for treatment, particularly in patients with a severe infection or one that is resistant to fluconazole."

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

[2] ITTm: Patients who received at least one dose of the study treatment and had a blood culture positive for *Candida* taken from a normally sterile site within 96 hours prior to inclusion in the study.

[3] Clinical success: resolution of the signs and symptoms of infection with *Candida spp*, no use of other systemic antifungals or additional oral fluconazole; improvement: incomplete resolution of the signs and symptoms of infection with *Candida*, no use of other systemic antifungals or additional oral fluconazole

3.2. New clinical data

In support of its application for re-assessment of the IAB, the company submitted results:
- from a subgroup analysis of the randomized, double-blind study of the non-inferiority of anidulafungin compared with fluconazole in non-neutropenic patients mainly with candidaemia (Reboli 2007);
- from an indirect comparison of antifungal treatments recommended for the management of invasive candidiasis (Mills 2009).

Data on the use of ECALTA are also reported by the company.

The Committee notes, on the other hand, that comparative clinical data are not always available versus amphotericin B or versus another echinocandin (caspofungin, micafungin) or versus voriconazole, nor is there information documenting the efficacy of anidulafungin in disseminated candidiasis.

Recommendations on the use of antifungals are also presented in the arguments put forward by the company. They are taken into account in the "Therapeutic use" section of this Opinion.

3.2.1. Subgroup analyses

The results of the study in the ITTm population are summarised and commented on in 3.1.

The subgroup analysis concerned patients classed as "severe" and defined as follows:

- intensive-care patients identified from hospital dossiers available for the 245 patients included in the study.
- patients with at least one organ dysfunction on inclusion; these patients were selected on the basis of the following criteria:
  - cardiac dysfunction defined as the prescription of a vasopressor within 24 hours prior to inclusion in the study;
  - renal dysfunction with creatinine clearance of < 30 ml/min or requiring dialysis on inclusion;
  - respiratory dysfunction with mechanical ventilation and/or documented respiratory failure;
  - liver dysfunction with bilirubinaemia twice as high as normal or ALAT, ASAT or alkaline phosphatase levels five times higher than normal.

The statistical analysis compared the success rates at the end of IV treatment using Fisher's test in the subgroups of interest. All-cause mortality was measured at 14 days and at 28 days by the same method.

Survival at 14 and 28 days was evaluated by the Kaplan-Meier method in the intensive care and/or organ dysfunction population.

Summary: the primary endpoint of the study was the success rate (clinical and microbiological) at the end of the IV treatment in the modified intention to treat population.

The secondary endpoints were survival and all-cause mortality at 14 and 28 days.

Results

The analysis covers 165 hospitalised patients who were in intensive care and/or had organ dysfunctions (63 intensive-care patients, 52 with renal dysfunction, 62 with respiratory failure, 85 with liver dysfunction and 33 with cardiac dysfunction).

Of these, 92 patients were randomised to the anidulafungin group, 73 to the fluconazole group.

There was no identifiable difference between the treatment groups as regards demographic and clinical characteristics.

No significant difference in response rates between the two arms was found in these different subgroups:

Response rates by patient subgroups

	Anidulafungin, n (%)	Fluconazole, n (%)	p value
Intensive-care patients	24/35 (68.6)	13/28 (46.4)	0.12
Renal impairment	22/28 (78.6)	15/24 (62.5)	0.23
Hepatic impairment	33/45 (73.3)	21/40 (52.5)	0.07
Respiratory failure	21/36 (58.3)	10/26 (38.5)	0.20
Cardiovascular failure	6/13 (46.2)	8/20 (40.0)	1.0

Shorr et al, 2008

No significant difference in 14-day survival of patients in intensive care and/or with organ dysfunction(s) was found between the two arms (Figure 2 Shorr et al 2008).

Overall, as the company says, "these results do not allow any conclusion to be drawn as to the superiority of anidulafungin or fluconazole in these subgroups of patients, in view of the methodological bias inherent in post-hoc subgroup analyses."

3.2.2. Indirect comparison

The meta-analysis[4] (indirect comparisons) is admissible by the Transparency Committee (methodology and statistical methods used).

- As regards the comparison of anidulafungin with fluconazole:

Given the architecture of the network of studies identified by Mills's meta-analysis, and that there is just one study directly comparing A vs F, the meta-analysis contributes nothing over and above the existing single study (Reboli et al 2007) that has already been analysed by the Transparency Committee in an earlier opinion.

- As regards the comparison of anidulafungin with other medicines used in the management of invasive candidiasis in adults:

The use of Mills's meta-analysis for this objective is questionable:

- The disparity between the studies (patient inclusion criteria, absence of neutropenia, yeast resistances, etc.) was not explained in detail in the publication,
- There are several instances of significant differences in therapeutic effects in the meta-analysis,
- The reference comparator was not always anidulafungin,
- The absence of any significant difference does not permit the conclusion that there is any equivalence between anidulafungin and medicines other than fluconazole, since the hypothesis tested in the meta-analysis was part of a "superiority" approach.

Thus, the change in comparator (the use of other medicines instead of fluconazole) does not seem justified merely from reading Mills's meta-analysis.

[4] Edward J Mills* et al. Antifungal treatment for invasive Candida infections: a mixed treatment comparison meta-analysis. Annals of Clinical Microbiology and Antimicrobials 2009;8:23 doi:10.1186/1476-0711-8-23

3.2.3. Other data

Data on use in countries in which ECALTA has been on the market for at least a year with an adequate level of sales were supplied and analysed by the company: in the European Union, these are Germany, Spain and Austria.

According to the company, these sales data show “that ECALTA is used not instead of fluconazole but in place of CANCIDAS. The marketing of ECALTA was not associated with any reduction in the number of days of treatment with fluconazole. Instead, it seems to have led to a reduction in the market share of CANCIDAS in terms of sales in the market for intravenous systemic antifungals: from 52 to 49% in Germany, 43 to 40% in Spain and 50 to 38% in Austria.”

Comments:

- Other antifungals may be prescribed is cases of invasive candidiasis in non-neutropenic patients, such as amphotericin B for severe forms and voriconazole for strains resistant to fluconazole.
- Invasive candidiasis covers a variety of clinical situations: neutropenic or non-neutropenic patients, severe forms (patient haemodynamically unstable according to IDSA), strains non-sensitive or resistant to fluconazole, etc.). The treatment strategy for use of the various antifungals takes account of the clinical setting (not just whether or not neutropenia is present).
- Practices may vary according to fungal ecology and local prescribing habits.

Overall, these (partial) sales data seem to be of little relevance in terms of identifying any change in the prescribing of antifungals for the management of invasive candidiasis since ECALTA went on the market.

3.3. Conclusion

The data submitted by the company do not provide any new clinical information that clarifies the role of anidulafungin in the management of adult patients with invasive candidiasis, particularly in cases with a strain resistant to fluconazole or in severe forms (with or without concomitant neutropenia).

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 rate it causes.

Public health benefit

Invasive candidiasis in non-neutropenic patients is a serious, life-threatening clinical condition which is a minor public health burden because of the limited number of patients involved.

The improvement of treatments for this form of invasive candidiasis and in particular for forms resistant to fluconazole and certain very severe forms is an important therapeutic need but does not constitute a priority public health need.

In the absence of any proof of the efficacy of ECALTA in patients with candidaemia that is resistant to fluconazole and in patients with deep, invasive candidiasis (endocarditis, osteomyelitis, meningitis), the transferability of the results of this study is not assured. In fact, the profile of patients for whom there is expected to be a need for a new antifungal does not correspond to the profile of the patients in the study. There is thus not expected to be any impact in terms of morbidity or mortality in this target population.

Consequently, there is not expected to be any benefit to public health from the medicinal product.

ECALTA is intended as a curative treatment.

Its efficacy/adverse effects ratio is high.

- In non-neutropenic adult patients, fluconazole is in most cases still the reference treatment, so that ECALTA is an alternative, like other echinocandins.

- If a strain resistant to fluconazole is suspected or if the patient has previously been exposed to azoles, voriconazole, echinocandins and liposomal amphotericin B are the treatments of choice. ECALTA has not been evaluated in these clinical settings or in cases of disseminated candidiasis.

The actual benefit of this medicinal product is substantial in the treatment of invasive candidiasis in non-neutropenic patients.

4.2. Improvement in actual benefit

In the absence of clinical data allowing this medicinal product to be positioned precisely in relation to medicines currently recommended for patient management, particularly in patients with a severe infection or one that is resistant to fluconazole, the Committee stands by its IAB rating of 16 April 2008, namely:

“In view of the modest difference observed in the magnitude of the effect compared with fluconazole, the non optimal level of evidence demonstrating superiority and the doubts as to the transferability of the results to real life, the Committee believes that the medicinal product ECALTA has not shown any improvement in actual benefit compared with fluconazole-based medicinal products with an adequate level of evidence (IAB V). It constitutes an additional therapeutic option the place of which in a treatment strategy needs to be clarified.”

4.3. Therapeutic use

Treatment strategies for systemic candidiasis in non-neutropenic adults

The consensus conference "Management of invasive aspergillosis and candidiasis in adults"[5] in 2004, discussed in the previous opinion, recommended the use of amphotericin B in the absence of renal failure (creatinine level < 1.5 times normal) or of fluconazole, except in neutropenic patients or those who have previously received fluconazole. In patients with renal impairment who have received fluconazole or are receiving at least 2 nephrotoxic treatments, caspofungin or liposomal amphotericin B are recommended. In patients with strains sensitive to fluconazole, a course of fluconazole is recommended, and in cases where the strain is resistant or has dose-dependent sensitivity, treatment with amphotericin B, voriconazole, caspofungin or liposomal amphotericin B is prescribed. In patients with candidaemia, the period of treatment is 2 weeks after the last positive blood culture. Removal of the intravascular catheter is recommended.

Since this consensus conference, updated recommendations from the US IDSA and recommendations from two groups of experts (one European, the other French) have been submitted by the company:

According to the US recommendations updated in 2009 by the IDSA (Infectious Diseases Society of America[6]):

- Fluconazole (800 mg followed by 400 mg/day) or an echinocandin (caspofungin 50 mg followed by 70 mg/day, micafungin 100 mg/day, anidulafungin 200 then 100 mg/day) is recommended as first-line treatment for adult patients (A-I). The panel of experts recommends an echinocandin for moderate to severe patients or those previously exposed to azoles (A-III). Fluconazole is recommended for less severe patients who have not previously been exposed to azoles (A-III).

- A switch from an echinocandin to fluconazole is recommended for patients infected with Candida that is sensitive to fluconazole (i.e. Candida albicans) and clinical stable (A-II).

- For infections with Candida glabrata, an echinocandin is recommended (B-III). A switch to fluconazole is recommended only if the strain's sensitivity has been confirmed (B-III). For patients who have previously received fluconazole or voriconazole and whose clinical condition has improved, with blood cultures returning to negative, treatment can be continued (B-III).

- For infections with Candida parapsilosis, treatment with fluconazole is recommended (B-III). For patients who have previously received an echinocandin and whose clinical condition has improved, with blood cultures returning to negative, treatment can be continued (B-III).

- Amphotericin B (0.5–1 mg/kg/day) or its lipid formulation (3-5 mg/kg) are alternatives in cases of intolerability or if other antifungals are not available (A-I). A switch from amphotericin B to fluconazole is recommended for patients whose isolates are sensitive to fluconazole and clinically stable (A-1).

- Voriconazole (400 mg then 200 mg twice a day) is effective for the treatment of candidaemia (A-1) but offers few advantages compared to fluconazole and is recommended as an oral course in cases of candidiasis with Candida krusei and Candida glabrata that are sensitive to voriconazole (B-III).

- The period of treatment recommended for candidaemia is two weeks after the blood cultures have returned to negative and the symptoms attributable to candidaemia have resolved (A-III).

- Removal of the catheter is strongly recommended in non-neutropenic patients (A-II).

[5] Joint SFAR, SPILF and SRLF consensus conference: Management of invasive aspergillosis and candidiasis in adults. Elsevier SAS. 2004.

[6] Pappas P, Kauffmann C, Andes D et al, Clinical Practice Guidelines for the management of candidiasis: 2009 update by the infectious disease society of America. Clinical Infectious Disease 2009 ;48: 503-535.

According to the recommendations of a group of European experts on the management of invasive candidiasis and candidaemia in adults in intensive-care units (Guery et al., 2008[7])

These recommendations are based on a review of the literature followed by a discussion by European experts. In haemodynamically unstable patients who are in septic shock or have signs of severe sepsis, a broad-spectrum antifungal with low toxicity is recommended. In these cases, echinocandins are the treatment of choice. A switch to fluconazole or voriconazole is recommended once the patient has been stabilised and the sensitivity of the species confirmed.

According to the recommendations on the correct use of antifungals in invasive candidiasis by the Committee of the State-owned hospitals of Paris (AP-HP) (COMAI, 2009[8])

In non-neutropenic patients, the first-line treatment is fluconazole "which can be used in most cases, except with severe forms or if the patient has previously been exposed to azoles. Otherwise, echinocandins[9] (caspofungin, micafungin, anidulafungin) and liposomal amphotericin B (AMBISONE) are the first-line treatments.

In addition,

"Because of the nephrotoxicity of liposomal amphotericin B, echinocandins are preferred with severe and haemodynamically unstable forms"

"Liposomal amphotericin B is to be preferred as first-line therapy if the presence of yeast other than Candida spp. is suspected (such as Cryptococcus)"

"The decision to use micafungin must take account of the potential risk of developing liver tumours. MYCAMINE should be used only if the administration of other antifungals is not appropriate."

Comments

These recommendations make no distinction between caspofungin, micafungin and anidulafungin in non-neutropenic adult patients. They take no account of the differences in their range of indications as per the European marketing authorisations and the levels of evidence of efficacy. Thus, in neutropenic patients and in paediatrics, the prescription of ECALTA, although recommended by the IDSA, is not validated by a European marketing authorisation.

- The place of anidulafungin (ECALTA) in the management of invasive candidiasis in adults

According to the opinion of 16 April 2008, "ECALTA could claim the same indications as caspofungin. However, unlike caspofungin, ECALTA does not have marketing authorisation for neutropenia. Its spectrum of activity in vitro gives reason to expect in vivo activity on *Candida non albicans*. However, there are limited clinical efficacy data for infections with *Candida albicans* that are resistant to fluconazole or to *Candida non albicans* (54 patients in study VER002-9)."

Note: In these situations, other echinocandins or voriconazole have better documented efficacy.

[7] Guery B, Arendrup M, Auzinger G et al, Management of invasive candidiasis and candidemia in adult non neutropenic intensive care unit patients: Part II. Treatment. Intensive Care Med. 2009; 35(2): 206-14.
[8] AP-HP COMAI, Invasive candidiasis/invasive aspergillosis. Treatment strategies. July 2009.
[9] At that time only caspofungin and micafungin were included on the non-GHS list.