HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

8 November 2006

VFEND 50 mg, film-coated tablets
B/28 (CIP: 3592886) B/56 (CIP: 3592892)

VFEND 200 mg, film-coated tablets
B/14 (CIP: 3592900) B/28 (CIP: 3592917) B/56 (CIP: 3592923)

VFEND 200 mg, powder for solution for infusion
Ampoule B/1(CIP: 3592946)

VFEND 40mg/ml, powder for oral suspension
Bottle (CIP: 3640616)

Applicant: PFIZER

Voriconazole
List I
Medicinal product requiring hospital prescription.

MA Date: 19 March 2002
MA (extension of indication): 10 January 2005

Reason for request: Inclusion on the list for use by hospitals in the extension of indication "**Treatment of candidaemia in non-neutropenic patients.**"

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient:

Voriconazole

1.2 Indication

VFEND (voriconazole) is a broad-spectrum triazole antifungal with the following indications:

- Treatment of invasive aspergillosis.
- **Treatment of candidaemia in non-neutropenic patients.**
- Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

VFEND should be administered primarily to patients with progressive, possibly life-threatening infections.

1.3 Dosage

VFEND film-coated tablets should be taken at least one hour before, or one hour after, a meal.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, before initiation and during voriconazole therapy.

Use in adults:
Therapy must be initiated with the specified loading dose of either the intravenous or oral form to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96 %), switching from the intravenous to the oral form is appropriate when clinically indicated.

Detailed information on dosage recommendations is given in the following table:

	Intravenous route	Oral route	
		Patients ≥ 40 kg	Patients < 40 kg
Loading Dose (first 24 hours	6 mg/kg every 12 hours	400 mg every 12 hours	200 mg every 12 hours
Maintenance Dose (after first 24 hours)	4 mg/kg twice daily	200 mg twice daily	100 mg twice daily

Dosage adjustment:
If patient response is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.

If patients are unable to tolerate treatment at these higher doses, they may be reduced in 50 mg steps to the maintenance dose of 200 mg twice daily, or 100 mg twice daily for patients less than 40 kg.

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 400 mg orally, twice daily (or 100 mg to 200 mg orally, twice daily in patients less than 40 kg).

Rifabutin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 350 mg orally, twice daily (or 100 mg to 200 mg orally, twice daily in patients less than 40 kg).

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly:
No dose adjustment is necessary in elderly patients.

Use in patients with renal impairment:
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no dosage adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Use in patients with hepatic impairment:
No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALAT, ASAT) (but continued monitoring of liver function tests for further elevations is recommended).

In patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND, it is recommended to use the standard loading dose regimens and halve the maintenance dose.

VFEND has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with hepatic impairment must be carefully monitored for drug toxicity.

Use in the child:
Safety and efficacy have not been established in children under the age of 2 years. Voriconazole is therefore not recommended in children aged less than two years.

The recommended dosage of maintenance treatment in children (from 2 to less than 12 years) is as follows:

	Intravenous route*	Oral route**
Loading dose	No oral or intravenous loading dose is recommended	
Maintenance dose	7 mg/kg twice daily	200 mg twice daily

* Based on a population pharmacokinetic analysis carried out in 82 immunodepressed patients aged from 2 to less than 12 years

** Based on a population pharmacokinetic analysis carried out in 47 immunodepressed patients aged from 2 to less than 12 years.

Use in children aged from 2 to less than 12 years with hepatic or renal insufficiency has not been studied.

These paediatric dose recommendations are based on studies in which VFEND was administered as the powder for oral suspension. Bioequivalence between the powder for oral suspension and tablets has not been studied in a paediatric population. Considering the likely limited gastro-enteric transit time in paediatrics, the absorption of the tablets may be different in children than in adult patients. For this reason it is recommended to use the oral suspension form in children aged 2 to less than 12 years.

Adolescents (from 12 to 16 years): use the same dosages as adults.

2 SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2005)

J - General antiinfective for systemic use
J02 - Systemic antimycotic
J02A - Systemic antimycotic
J02AC - Triazole derivatives
J02AC03 - Voriconazole

2.2 Medicines in the same therapeutic category

These are triazole derivatives (ATC class J02AC) indicated in *Candida* infections:

TRIFLUCAN Fluconazole

2.3 Medicines with a similar therapeutic aim

These are the systemic antifungal drugs indicated in *Candida* infections:

FUNGIZONE Amphotericin B
ABELCET Lipid Amphotericin B
AMBISOME Liposomal Amphotericin B
ANCOTIL Flucytosine
CANDIDAS Caspofungin

3 ANALYSIS OF AVAILABLE DATA

Three studies were provided in the dossier.

The non-comparative studies 150-309/604 which evaluated the efficacy and safety of voriconazole in the treatment of refractory candidiasis were not taken into account.

Study 150-603[1] comparing voriconazole with liposomal amphotericin B in the empirical treatment of fungal infections in patients treated by chemotherapy, haematopoietic stem cell recipients, or neutropenic patients, was not taken into account. As the populations concerned were only a sub-group of the population for whom the MA was granted, the results of these studies cannot be extrapolated to the whole population of non-neutropenic patients with candidaemia. No conclusions may be drawn because of the small number of patients with candidaemia (N=8) enrolled in study 150-603.

Only study 150-608[2] is described in this opinion.

3.1 Efficacy

Study 150-608:

Objective:
This was an open, randomized, comparative study.

The primary objective of this non-inferiority study was to compare the efficacy and safety of voriconazole to the conventional strategy: amphotericin B followed by fluconazole in the treatment of candidaemia in non-neutropenic patients.

Inclusion criteria:
Subjects aged 12 years or more presenting:

- At least one positive blood culture for Candida during the 96 hours before randomization and
- Clinical proof of infection for at least 48 hours before enrolment (temperature > 37.8°C twice at 4 hour intervals or > 38.6°C a sing le time, systolic blood pressure < 90 mmHg or a fall of 30 mmHg compared to the baseline value, signs of inflammation of a site infected by *Candida*).

Exclusion criteria:

- Subjects with a history of allergy or intolerance to antifungal azole derivatives or amphotericin B,
- Subjects with a neutrophil count < $0.5x10^9$/L,
- Subjects with aplastic anaemia, chronic septic ganulomatosis, AIDS,
- Subjects with moderate or severe hepatic disease (alkaline phosphatase, alanine amino-transferase, aspartate aminotransferases or total bilirubin levels more than 5 times the normal value),
- Subjects with severe renal insufficiency (creatinemia > 220 µmol/L),
- Pregnant women,
- Subjects with a poor chance of surviving for 24-hours,

[1] Walsh TJ et al., liposomal Voriconazole compared with amphotericin B for empirical antifungal therapy in patients with neutropenia and persists fever, *NEJM,* 2002, 346 (4), 225-34

[2] BJ Kullberg et al. Voriconazole versus regimen of amphotericin B followed by fluconazole for candidaemia in-neutropenic patients: a randomized non-inferiority trial. www.thelancet.com. Published online October 12, 2005 DOI:10.1016/S0140-6736(05)67490-9.

- Subjects with documented failure of anti-fungal treatment for the same *Candida* infection,
- Subjects previously treated by an antifungal agent during the 96 hours before inclusion.
- Subjects treated by medicinal products interacting with antifungal azole derivatives.

Number of subjects:
Four hundred and twenty-seven patients were randomized in a 2:1 ratio to receive treatment by voriconazole (n= 283) or amphotericin B/fluconazole (n=139).

Efficacy was evaluated for the modified intention-to-treat population (mITT): patients with at least a one blood culture positive for *Candida* during the 96 hours before randomization and who received at least one dose of treatment.

Voriconazole group mITT n=248, amphotericin B/fluconazole group mITT n=122.

Safety was evaluated in patients who received at least one dose of the study treatment.

Treatment:
The patients in the voriconazole group were treated intravenously for at least 3 days with the dose of 6mg/kg every 12 hours for 24 hours, then 3 mg/kg every 12 hours. After 3 days the patients could switch to oral dosing. The oral dose was 200 mg twice daily.

Patients in the amphotericin B/fluconazole group received 0.7–1.0 mg/kg/day of amphotericin B every 2 to 6 hours. Amphotericin B could be followed by oral or IV fluconazole treatment at the dose of 400 mg/day after not less than 3 days and not more than 7 days of amphotericin B treatment.

The exceptions were as follows:
- Patients not tolerating 3 days of treatment with amphotericin B could switch to fluconazole (IV/oral) earlier.
- If the isolated *Candida* species was considered to be resistant to fluconazole, amphotericin B treatment could be prolonged for more than 7 days.

The total duration of treatment was at least two weeks after the last positive blood culture and not more than 8 weeks. Patient follow-up continued for 12 weeks after the end of the treatment.

Primary endpoint:
The response to treatment was evaluated by a Data Review Committee blinded to study medication.

The success rate was defined by the resolution or improvement in all the clinical symptoms of the infection with eradication of *Candida* from the blood and deep infected tissue sites 12 weeks after end of therapy (EOT).

Secondary endpoints:
- Success rate at the last relevant evaluation time defined by the Data Review Committee: EOT, 2, 6 or 12 weeks after EOT.
- Survival 98 days after randomization.

Statistical analysis:
For the efficacy analysis, the success rate at 12 weeks was compared between the two treatment groups in the mITT population.

Voriconazole was to be considered non-inferior to amphotericin B/fluconazole if the lower limit of the 95% confidence interval of the difference between the success rates of the two treatments at 12 weeks after EOT was greater than -15%.

Results:
Patient characteristics at baseline were similar except for the mean APACHE II score, which was higher in patients treated by amphotericin B/fluconazole than in patients treated by voriconazole (14.7 vs 13.8).

At baseline, 61% of the patients in the voriconazole group and 50% of the patients in the amphotericin B/fluconazole group were infected by *non albicans Candida* species.

In the mITT population, the success rates stratified by geographical area were 41% with voriconazole and 41% with amphotericin B/fluconazole, with a confidence interval of the difference between the two groups of CI_{95} [-10.6%; 10.6%].

As the lower limit of the confidence interval was greater than -15%, the non-inferiority of voriconazole compared to amphotericin B followed by fluconazole was demonstrated.

Secondary endpoints:
In the mITT population, the success rate at the last evaluation time was 65.5% in the voriconazole group and 71.3% in the amphotericin B/fluconazole group.

The difference stratified by geographical area was -5.6% CI_{95}[-15.8% ; 4.2%]. Non-inferiority was not therefore demonstrated.

In the mITT population, mortality on day 98 was 36 % (88 patients) in the voriconazole group and 42% (51 patients) in the amphotericin B/fluconazole group.

RR = 0.82; CI_{95} [0.58 ; 1.16], non-significant difference.

3.2 Adverse effects

The median duration of treatment was 15 days in the two treatment groups.

Safety was evaluated for the 403 patients who received at least one dose of the study treatment.

The incidence of serious adverse events was higher in the amphotericin B/fluconazole group (57%) compared to that of the voriconazole group (46%) (p=0.048). The incidence of treatment-related adverse events was 36% in the voriconazole group and 51% in the amphotericin B/fluconazole group (p=0.003).

No significant difference was observed between the two treatment groups for hepatic adverse events and skin rashes. On the contrary, the incidence of renal events was higher in the amphotericin B/fluconazole group than in the voriconazole group (21% vs 8% p=0.0002).

3.3 Conclusion

Three hundred and seventy non-neutropenic patients (aged over 12 years) with documented candidaemia were enrolled in an open, comparative study; 248 were treated by voriconazole and 122 by amphotericin B followed by fluconazole. The median duration of treatment was 15 days in the two treatment arms.

The response to treatment was evaluated by a Data Review Committee. The success rate was defined by the resolution or improvement in all clinical symptoms of the infection with eradication of *Candida* from the blood and infected deep tissue sites 12 weeks after the end of therapy. Patients in whom no evaluation was made 12 weeks after the end of the treatment were considered to be failures.

The modified intention-to-treat analysis showed the non-inferiority of voriconazole compared to amphotericin B/fluconazole in the treatment of candidaemia.

In terms of safety, the treatment groups were globally similar. However, the incidence of renal events was higher in the amphotericin B/fluconazole group than in the voriconazole group. However, visual disorders and the rate of treatment discontinuations due adverse events were higher in the voriconazole group.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

The disorders concerned by these proprietary drugs are immediately life-threatening or may cause fatal complications.

These proprietary drugs are intended to be used for curative treatment.

The efficacy/adverse effects ratio for these proprietary drugs is high.

Public Health benefit:

Candidaemia in non-neutropenic patients is a serious and life-threatening clinical situation which constitutes a low public health burden because of the small number of patients concerned.

The improvement in the treatment of candidaemia and in particular fluconazole-resistant forms is an important therapeutic requirement although it does not constitute a public health priority.

A review of the available data and existing treatments, shows that this proprietary drug may be expected to have an impact in terms of renal safety which can be only be qualified as very slight.

Accordingly, this proprietary drug is not expected to have an impact on public health.

The actual medical benefit of these proprietary drugs is substantial.

4.2 Improvement in actual benefit

VFEND provides a minor improvement in medical benefit (IAB IV) in terms of safety compared to FUNGIZONE in the treatment of candidaemia in non-neutropenic patients, for *Candida* strains resistant to TRIFLUCAN.

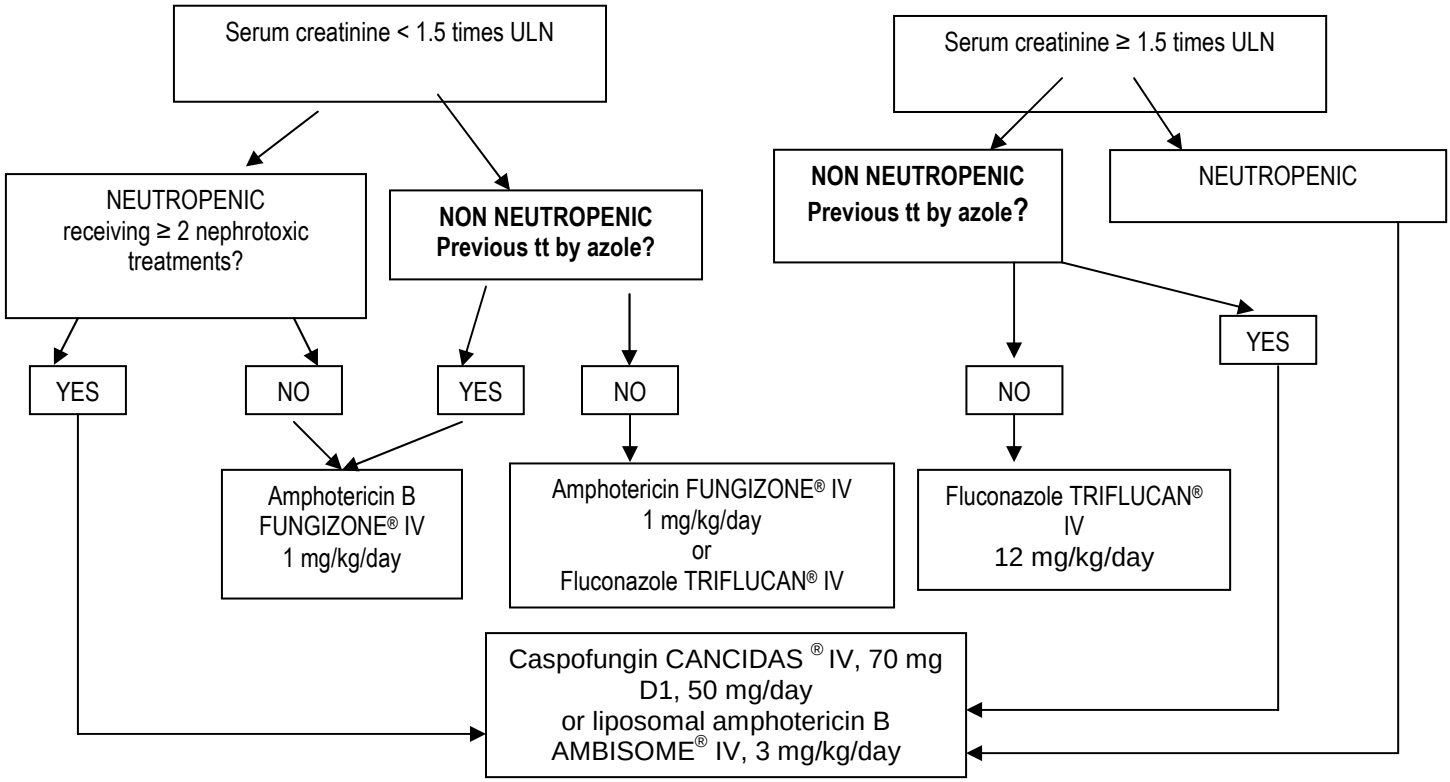
4.3 Therapeutic use[3]:

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

Therapeutic strategy in systemic candidiasis

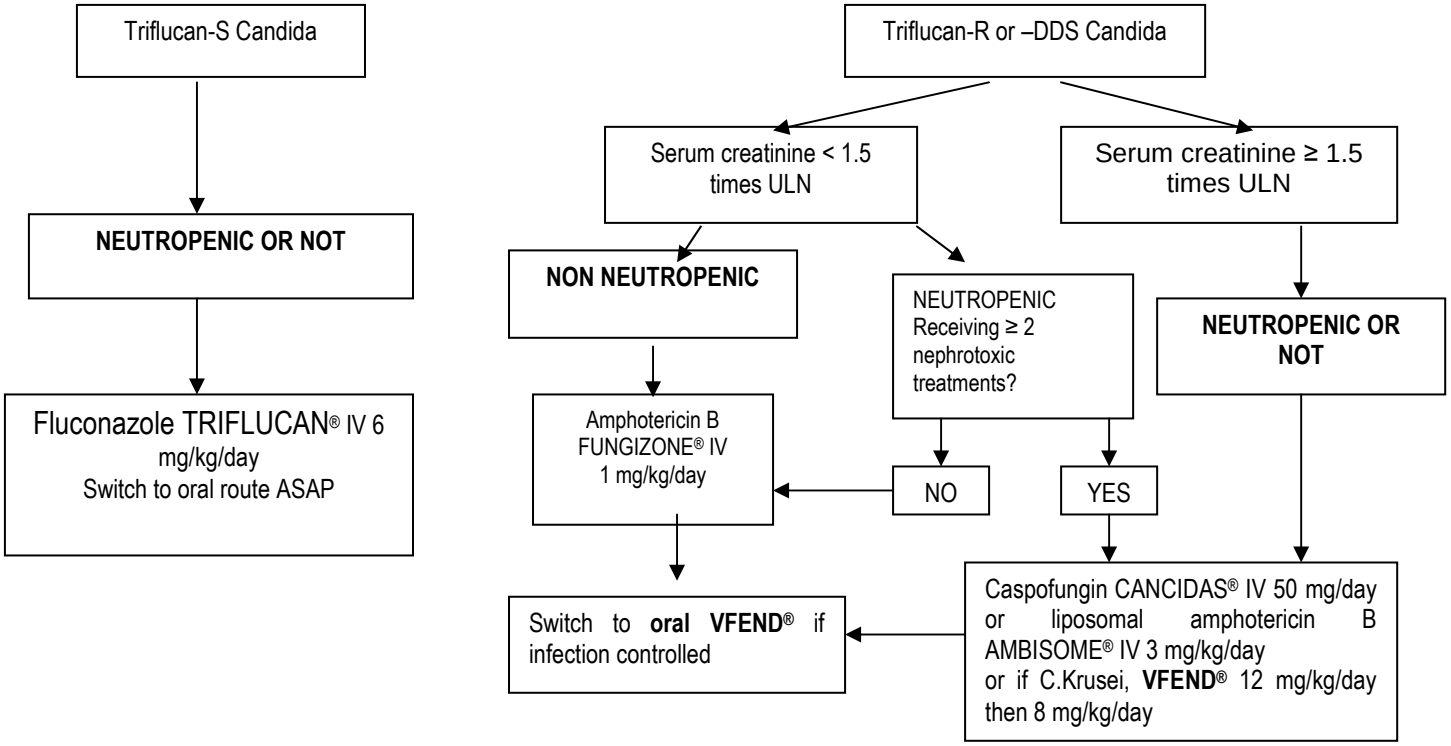
Therapeutic strategies according to gender and species after isolation of a yeast and before or after identification of the species are described in the decision trees presented below.

Figure 1: Therapeutic strategy after isolation of a yeast and before identification of the species



[3] SFAR, SPILF, SRLF, Common consensus conference: Management of invasive candidiasis and aspergillosis in adults, 2004

Figure 2: Therapeutic strategy after identification of the Candida species



S: Sensitive
DDS: Dose-dependent sensitivity
R: Resistant

Specific features of treatment of candidaemia

- The total duration of treatment is two weeks after the last positive blood culture and the disappearance of symptoms or at least 7 days after the correction of the neutropenia.
- Withdrawal of the intravascular catheter is recommended.

The 2004 consensus conference therefore recommended the use of amphotericin B in the treatment of candidaemia in non-neutropenic patients in the absence of renal insufficiency, or fluconazole except in patients who have received it previously. In patients with renal impairment who have received fluconazole or who are receiving at least 2 nephrotoxic treatments; caspofungin or liposomal amphotericin B is recommended. If the strain is found to be sensitive to fluconazole, a switch to fluconazole is recommended and if the strain is found to be resistant or to have a dose-dependent sensitivity, treatment by amphotericin B, voriconazole, caspofungin or liposomal amphotericin B is prescribed.

4.4 Target population

The incidence of candidaemia may be estimated to be between 0.20[4] and 0.29[5] cases per 1000 admissions.

According to the study of Richet[5] on the incidence of candidaemia, the proportion of non-neutropenic patients may be estimated to be 77%.

The number of stays of more than 24 hours in Obstetric Surgery Medicine (OSM) departments in 2004 in private and public hospitals was 9,862,000[6].

According to these data, the incidence rate of candidaemia may be estimated to be between 1,973 and 2,860/year.

The target population corresponding to the indication "treatment of candidaemia in non-neutropenic patient" may therefore be estimated to be between **1,520** and **2,202** cases/year.

4.5 Recommendations of the Transparency Committee

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

4.5.1 Containers: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65%

[4] TORTORANO A.M, PEMAN J, BERNHARDT H, KLINGSPOR L, KIBBLER C.C, FAURE O, BIRAGHI E, CANTON E, ZIMMERMANN K, SEATON S, GRILLOT R, the ECMM Working Group on Candideamia, Epidemiology of candideamia 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

[5] RICHET H, ROUX P, DES CHAMPS C, ESNAULT Y, Candidemia in French Hospitals: incidence rates and characteristics, Clin Microbiol Infect, 2002, 8: 405-412

[6] DREES. L'activité des établissements de santé en 2004 en hospitalisation complète et partielle. N°456, December 2005.