HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

12 November 2008

MYCAMINE 50 mg, powder for solution for infusion
Pack of 1 vial (CIP: 386 627-2)

MYCAMINE 100 mg, powder for solution for infusion
Pack of 1 vial (CIP: 386 628-9)

Applicant: ASTELLAS PHARMA SAS

Micafungin

ATC Code: J02AX05

List I
Medicinal product for hospital prescription only

Marketing Authorisation (MA) date: 25 April 2008 (centralised procedure)

Reason for request: Inclusion on the list of medicinal products approved for institutional use by hospitals.

Medical and Economic Evaluation and Public Health Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Micafungin

1.2. Indication

"MYCAMINE is indicated for:

Adults, adolescents ≥ 16 years of age and elderly:

- Treatment of invasive candidiasis.
- Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.
- Prophylaxis of *Candida* infections in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for at least 10 days.

Children (including neonates) and adolescents <16 years of age:

- Treatment of invasive candidiasis.
- Prophylaxis of *Candida* infections in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for 10 or more days.

The decision to use MYCAMINE should take into account a potential risk for the development of liver tumours (see section 4.4 of the SPC). MYCAMINE should therefore only be used if other antifungals are not appropriate".

1.3. Dosage

"Consideration should be given to official/national guidance on the appropriate use of antifungal agents.
Treatment with MYCAMINE should be initiated by a physician experienced in the management of fungal infections.
Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

The dose regimen of MYCAMINE depends on the body weight of the patient as given in the following tables:

Use in adults, adolescents ≥ 16 years of age and elderly

Indication	**Body weight > 40 kg**	**Body weight ≤ 40 kg**
Treatment of invasive candidiasis.	100 mg/day*	2 mg/kg/day*
Treatment of oesophageal candidiasis	150 mg/day	3 mg/kg/day
Prophylaxis of *Candida* infections	50 mg/day	1 mg/kg/day

** If the patient's response is inadequate, e.g. persistence of positive cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg*

Duration of treatment

Invasive candidiasis: The treatment duration of *Candida* infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and ***after*** resolution of clinical signs and symptoms of infection.

Oesophageal candidiasis: For the treatment of oesophageal candidiasis, MYCAMINE should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of *Candida* infections: For prophylaxis of Candida infection, MYCAMINE should be administered for at least one week after neutrophil recovery.

Use in children (including neonates) and adolescents < 16 years of age

Indication	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis.	100 mg/day*	2 mg/kg/day*
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

**If the patient's response is inadequate, e.g. persistence of positive cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg*

Duration of treatment
Invasive candidiasis: The treatment duration of *Candida* infection should be at least 14 days. Antifungal treatment should continue for at least one week after two successive negative blood cultures have been obtained and ***after*** resolution of clinical signs and symptoms of infection.

Prophylaxis of *Candida* infections: For prophylaxis of *Candida* infection, MYCAMINE should be administered for at least one week after neutrophil recovery.
Experience with Mycamine in patients under 2 years of age is limited.

Gender/Ethnic group
No dose adjustment is necessary based on gender or ethnic group (see section 5.2 of the SPC).

Use in patients with hepatic impairment
No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see section 5.2 of the SPC). There are currently insufficient data available for the use of MYCAMINE in patients with severe hepatic impairment and its use is not recommended in these patients (see section 4.4 of the SPC).

Use in patients with renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 5.2 of the SPC).

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour. More rapid infusions may result in more frequent histamine-mediated reactions.

For reconstitution instructions see section 6.6 of the SPC".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

J : general anti-infectives for systemic use
J02 : systemic antimycotics
J02A : systemic antimycotics
J02AX : other systemic antimycotics
J02AX05 : micafungin

2.2. Medicines in the same therapeutic category

The indications of MYCAMINE are not strictly identical to those of the other antifungal agents of the echinocandin class (CANCIDAS, ECALTA). In addition, MYCAMINE is the first antifungal in the echinocandin class with a marketing authorisation in paediatric use.

Antifungals in the echinocandin class

INN	Proprietary name	Indications
Caspofungin **IV form**	CANCIDAS 50 mg CANCIDAS 70 mg	1) Treatment of invasive candidiasis in adult patients. 2) Treatment of invasive aspergillosis in adult patients who are refractory to or intolerant of amphotericin B, lipid amphotericin B formulations and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy. 3) Empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus)* in febrile, neutropenic adult patients.
Anidulafungin **IV form**	ECALTA 100 mg	"Treatment of invasive candidiasis in non-neutropenic adult 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."

2.3. Medicines with a similar therapeutic aim

- **Treatment of invasive candidiasis**

IV forms, indicated in adults and children
- ABELCET (amphotericin B lipid complex), concentrate for dilution for IV infusion
- AMBISOME (liposomal amphotericin B), powder for liposome suspension for IV infusion
- FUNGIZONE (amphotericin B), powder for injection
- TRIFLUCAN (fluconazole), solution for infusion
- VFEND (voriconazole), powder for IV infusion (children from 2 years)

Oral forms, indicated in adults and children
- FUNGIZONE (amphotericin B), capsules/oral suspension
- TRIFLUCAN (fluconazole), capsules/powder for oral suspension
- VFEND (voriconazole), tablet/powder for oral solution (children from 2 years)

- **Treatment of oesophageal candidiasis in adults**

IV form
- TRIFLUCAN (fluconazole), solution for infusion

Oral forms
- NOXAFIL (posaconazole) oral suspension
- SPORANOX (itraconazole), oral solution
- TRIFLUCAN (fluconazole), capsules/powder for oral suspension

- **Prophylaxis of *Candida* infections in patients (adults and children)**

Systemic antifungal medicinal products with indications for prophylaxis:

Medicinal products	Indications (MA)
TRIFLUCAN (fluconazole) - Infusion - Capsule - Oral suspension	Prophylaxis of infections due to susceptible Candida strains in adults who are considered at risk of prolonged and severe neutropenia, during induction and consolidation treatments for acute leukaemia and during haematopoietic stem cell transplantation.
Oral FUNGIZONE (amphotericin B) - Capsule - Oral suspension	Prevention of candidiasis in subjects at very high risk (preterm infants, immunocompromised patients or patients undergoing antineoplastic chemotherapy)
NOXAFIL (posaconazole) - Oral suspension	Prophylaxis of invasive fungal infections in the following patients (adults): - Patients receiving remission-induction and consolidation chemotherapy for acute myeloid leukaemia or myelodysplastic syndromes expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections. - Haematopoietic stem cell transplant recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.
NIZORAL* (ketoconazole) - tablet	Prophylaxis of fungal infections in patients with congenital or acquired immune depression (indication restricted to infections due to susceptible micro-organisms)
SPORANOX (itraconazole) - oral solution, capsule - Infusion	No MA for prophylaxis**
VFEND (voriconazole) - tablet - Infusion	No MA for prophylaxis**

* Actual benefit insufficient in this indication

**Nevertheless in France, these proprietary medicines are sometimes used for prophylaxis.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of micafungin was evaluated in 5 phase III, randomised, double-blind, controlled non-inferiority studies versus active comparators.

3.1.1. Characteristics of the studies

Experimental Design*	Treatment regimen (1 daily dose by infusion over 1 hour)	Groups and Number of patients
Treatment of the candidaemia/invasive candidiasis		
Study FG 463-21-08 Controlled non-inferiority study (delta 15%): micafungin vs. liposomal amphotericin B, in adults and paediatric patients with confirmed candidaemia or invasive candidiasis.	- Micafungin: 100 mg to 200 mg/day for patients weighing >40 kg and 2.0 mg/kg to 4 mg/kg/day for those weighing ≤40 kg. - Amphotericin B: 3 mg/kg to 5 mg/kg/day. A 50% reduction in the dose was indicated in the case of nephrotoxicity after at least three days of treatment. Duration of treatment: not less than 14 days and not more than 4 weeks (8 weeks in the case of disseminated chronic candidiasis or *Candida* endophthalmitis).	- micafungin 100 mg 264 adults 52 children - amphotericin B 267 adults 54 children
Etude 03-0-192 Controlled non-inferiority study (delta 15%): micafungin (2 dosage strengths) vs. caspofungin in adults with confirmed candidaemia or invasive candidiasis.	- Micafungin in two groups: 100 mg/day or 150 mg/day - Caspofungin: loading dose of 70 mg on D1, then 50 mg/day. Patients on caspofungin could switch to fluconazole after 10 doses of caspofungin. Duration of treatment: not more than 4 weeks (8 weeks in the case of chronic disseminated candidiasis or *Candida* endophthalmitis).	- micafungin 100 mg 191 adults - micafungin 150 mg: 199 adults - caspofungin 50 mg 188 adults
Treatment of oesophageal candidiasis (OC)		
Etude 03-7-005 Controlled non-inferiority study (delta 10%): micafungin vs. fluconazole in adults with OC.	- Micafungin: 150 mg/day - Fluconazole : 200 mg/day Duration of treatment: at least 14 days or 7 days after resolution of all clinical symptoms of OC (maximum 42 days).	- micafungin 150 mg/day 260 adults - fluconazole 200 mg/day 258 adults
Etude 03-7-008** Controlled non-inferiority study: micafungin vs. fluconazole in adults with OC.	- Micafungin: 150 mg/day - Micafungin: 300 mg alternating every two days with a placebo solution - Caspofungin: 50 mg/day Duration of treatment: at least 14 days or 7 days after resolution of all clinical symptoms of OC (maximum 28 days).	- micafungin 150 mg/day 151 adults -micafungin 300 mg/2 days 149 adults - caspofungin 50 mg/day 152 adults
Prophylaxis of Candida fungal infections		
Etude 98-0-050 Controlled non-inferiority study (delta threshold = 10%): micafungin vs. fluconazole in adult and paediatric stem cell transplant recipients.	- Micafungin: 50 mg/day (1 mg/kg/day for weight <50 kg) - Fluconazole 400 mg/day (8 mg/kg/day for weight <50 kg) Duration of treatment: at least until establishment of the graft (neutrophils ≥ 500/mm^3), not more than 42 days after transplantation or until the occurrence of proven, probable or suspected invasive fungal infection.	- micafungin 50 mg/day 386 adults 39 children - fluconazole 400mg/day 412 adults 45 children

* The exclusion criteria included patients with severe hepatic impairment (defined by transaminase levels > 10 times the upper limit of normal - ULN - and bilirubin levels > 5 times the ULN)

** The results of this study will not be presented as caspofungin does not have Marketing Authorisation in France in this indication.

3.1.2. Study Results

- **Candidaemia/Invasive candidiasis**

Study FG 463-21-08: Micafungin vs. liposomal amphotericin B[1]

The demographic and medical characteristics of patients were similar in the two treatment groups.

Adult population: the median age of patients was 54.5 years (18 - 89) in the micafungin group versus 56 years (16 - 97) in the amphotericin B group. Most patients (72% vs. 76%) had an Apache II score ≤ 20 (mean score: 15.8 ± 8.4 vs. 15.6 ± 8.1) and candidaemia (83% vs. 84%) and a few patients had invasive candidiasis (17%) or neutropenia (13% vs. 11%). The principal underlying diseases were: blood disorders (19% vs. 14%), solid organ tumour (14% vs. 20%) and diabetes (12%). *Candida albicans* was the most frequently isolated pathogenic agent (39 % vs. 43 %). The most frequently non-*albicans* Candida species isolated were: *C. tropicalis* (26 % vs. 24 %), *C. parapsilosis* (16 % vs. 15 %), *C. glabrata* (12 % vs. 8 %),) and *C. krusei* (3% vs. 4%).

Paediatric population: the mean age of patients was 3.1 years (<1 – 14) in the micafungin group versus 2 years (<1 - 15) in the amphotericin B group. Most patients had candidaemia (93% . 95%) and a few patients had invasive candidiasis (7% vs. 5%) or neutropenia (12% vs. 24%). The main underlying pathologies were: haematological malignancy (20% vs. 14%), premature birth (22% vs. 17%) and gastrointestinal disorders (22% vs. 18 %). C*andida albicans* (39 % vs. 33 %) and *C. parapsilosis* (27% vs. 33%) were the most commonly isolated pathogenic agents.

The median duration of treatment was 14 days.

Results

The primary endpoint was overall treatment success: clinical response (complete or partial response)[2] and mycological response (eradication or suspected eradication) evaluated by the investigator at the end of intravenous therapy.

Micafungin was considered to be non-inferior to liposomal amphotericin B if the lower limit of the confidence interval of the difference (Micafungin - Ampho B) was greater than -15%.

- **Overall treatment success rate**

	Micafungin		**Liposomal amphotericin B**		**Difference % [95% CI]**
	N	**n (%)**	**N**	**n (%)**	
Adult population					
Overall treatment success ***(PP population)***	**202**	**181 (89.6)**	**190**	**170 (89.5)**	**0.1 [- 5.9 ; 6.1]**
No neutropenia at baseline	178	163 (91.6)	175	158 (90.3)	0.7 [-5.3 ; 6.7]*
Neutropenia at baseline	24	18	15	12	
Overall treatment success (***mITT population***)	**247**	**183 (74.1)**	**247**	**172 (69.6)**	**4.5 [-3.5 ;12.4]**
Paediatric population §					
Overall treatment success (***PP population***)	**41**	**35 (85.4)**	**42**	**37 (88.1)**	**- 2.7 [-17.3 ;11.9]**
Overall treatment success (***mITT population***)	**52**	**36 (69.2)**	**54**	**40 (74.1)**	**- 4.8 [-22.0 ;12.3]**
<2 years	26	21	31	24	
Premature infants	10	7	9	6	
Neonates (0 - <4 weeks)	7	7	5	4	

* difference adjusted according to neutropenia status

§ This analysis should be considered as indicative because of the small number of paediatric patients included in the study; the statistical power was insufficient to be able to draw any conclusions.

The success rates observed in the adult population (PP and mITT analysis) showed a non-inferiority of micafungin compared to liposomal amphotericin B in the study population. However,

[1] Kuse ER et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet, 2007 ; 369 (9572): 1519-1527*

[2] *Complete* response: resolution of all signs or symptoms ascribable to the fungal infection, including radiographic abnormalities associated with the infection if these were present at baseline; *Partial* response : Improvement in signs or symptoms ascribable to the fungal infection, including radiographic abnormalities associated with the infection if present at baseline:

because the numbers of patients with invasive candidiasis and neutropenia were very small, it was not possible to draw any conclusions regarding these more severe infections.

Study 03-0-192: Micafungin (100 mg and 150 mg) vs. Caspofungin[3]

Populations

The demographic and medical characteristics of patients were similar in the three treatment groups. The median age of patients was approximately 57 years (18 – 95). Most patients (80%) had an Apache II score ≤ 20 (mean score: 15), candidaemia (83 %) and few patients had invasive candidiasis (approximately 15%) or neutropenia (8%). The main underlying pathologies were (approximately 30%): diabetes, bacteraemia and renal failure. *Candida albicans* was the most frequently isolated pathogenic agent (49% vs. 44%). The most frequently isolated non-*albicans* Candida species were: *C. tropicalis* (16% vs. 17%), *C. parapsilosis* (13% vs. 22%), *C. glabrata* (15% vs. 17%) and *C. krusei* (4% vs. 2%). The median duration of treatment was 14 days.

Results

The primary endpoint was overall treatment success: clinical responses (complete or partial) and mycological response (eradication or presumed eradication) evaluated by the investigator at the end of intravenous therapy.

Micafungin could be considered to be non-inferior to Caspofungin if the lower limit of the confidence interval of the difference (Micafungin - Caspofungin) was greater than -15%.

- **Overall treatment and mycological success rates**

	Micafungin 100 mg	**Micafungin 150 mg**	**Caspofungin 50 mg**
Per protocol population (PP)	**N=164**	**N=177**	**N=162**
Success	135 (82.3%)	129 (72.9%)	125 (77.2%)
Difference between treatments*	5.2	- 4.3	
95% CI	[-3.3 ; 13.3]	[-12.5 ; 4.9]	
Intention-to-treat population - ITT	**N=199**	**N=202**	**N=192**
Success	147 (73.9%)	142 (70.3%)	137 (71.4%)
Difference between treatments*	2.5	- 1.1	
95.0% CI	[-5.9 ; 11.0)	[-9.3% ; 7.8%]	

** Micafungin minus caspofungin.*

The success rates observed supported the non-inferiority of micafungin compared to caspofungin. It should be noted that very few patients were affected by invasive candidiasis and neutropenia.

- **Oesophageal candidiasis: Micafungin *versus* Fluconazole (Study 03-7-005)[4]**

Populations

The demographic and medical characteristics of patients were comparable in the two treatment groups.

The mean age of enrolled patients was 37 years (17 – 80 years) in the micafungin group and 37.5 years (17 - 87) in the fluconazole group. The main underlying pathology was HIV (94% vs. 93%) including approximately 60% with a median CD4 count <100 cells/ml; 8.5% of patients in the micafungin group and 11.6% in the fluconazole group were receiving antiretroviral medication. *Candida albicans* was the pathogenic agent most frequently isolated at baseline (98% of cases).

[3] Pappas et al. Micafungin versus caspofungin for treatment of candidaemia and other forms of invasive candidiasis. *CID 2007;45:883–93*

[4] De Wet E et al. A randomised, double blind, comparative trial of micafungin (FK463) vs. fluconazole for the treatment of oesophageal candidiasis N. T. *Aliment Pharmacol Ther 2005; 21: 899–907.*

Results
The primary endpoint was treatment success defined by an endoscopic score = 0 (disappearance of lesions, endoscopic cure) at the end of treatment.

Micafungin could be considered to non-inferior to fluconazole if the lower limit of the confidence interval of the difference (Micafungin - Fluconazole) was greater than -10%.

- **Endoscopic cure rates**

	Micafungin		**Fluconazole**		**Difference % [95% CI]**
	N	**n (%)**	**N**	**n (%)**	
PP Population	**189**	**183 (96.8)**	**192**	**182 (94.8)**	**2.0 [- 2.0 ; 6.0]**
ITT Population	**260**	**228 (87.7)**	**258**	**227 (88.0)**	**- 0.3 [-5.9 ; 5.3]**
Mycological eradication	260	179 (68.8)	258	189 (73.3)	NS
Relapse after 2 - 4 weeks	30/198 (15.2)		22/195 (11.3)		NS

The results of this study demonstrated a non-inferiority of micafungin compared to fluconazole.

- **Prophylaxis of Candida fungal infections in patients undergoing haematopoietic stem cell transplantation**

Study 98-0-050: Micafungin versus Fluconazole[5]

Populations

Eight hundred and eighty-two patients were randomised to receive double-blind either micafungin (n= 425) or fluconazole (n=457). The mean age of included patients was 43 years (range: 0.6 - 73), including 9.5% (84/882) <16 years and 6.3% (56/882) >65 years.
At baseline, 52% (220/425) of the patients in the micafungin group and 56% (256/457) in the fluconazole group had received an allogeneic graft and 48% versus 44% an autologous or syngenic graft. Approximately 22% of patients developed a graft-versus-host reaction (GVH) with a median time to onset of 20 days.
The most frequent underlying pathologies were, in the adult population, non-Hodgkin's lymphoma (26%), multiple myeloma (22%), acute myeloid leukaemia (13%) and chronic myeloid leukaemia (12%); in the paediatric population they were acute lymphoid leukaemia (micafungin: 38% vs. fluconazole: 24%) and acute myeloid leukaemia (18% vs. 27%). Approximately 30% of patients had fungal colonisation at baseline, mainly by *C. albicans* (71% vs. 60%) and *C. glabrata* (10% vs. 13%).

The mean duration of treatment was 19 days (max. 51 days).

Results
The primary endpoint was overall treatment success defined by an absence of proven, probable or suspected systemic fungal infection during treatment and during the follow-up period (4 weeks after treatment).

Micafungin could be considered to be non-inferior to fluconazole if the lower limit of the confidence interval of the difference (Micafungin - Fluconazole) was greater than -10%. Superiority was deemed to be established if the lower limit of the confidence interval of the difference was positive.

[5] Van Burik et al. Micafungin versus Fluconazole for Prophylaxis against Invasive Fungal Infections during Neutropenia in Patients Undergoing Hematopoietic Stem Cell Transplantation. *CID 2004;39:1407–16*

- **Treatment success rates**

	Micafungin	Fluconazole	Difference [95% CI]
Total			
ITT Population	**340/425 (80.0%)**	**336/457 (73.5%)**	**6.5 [0.9 ; 12.0]**
PP* Population	322/397 (81.1%)	321/433 (74.1%)	7. 0 [1.3 ; 12.6]
Type of graft			
Allograft	**157/220 (71.4%)**	**175/256 (68.4%)**	**3.0 [- 5.3 ; 11.3]**
isograft or autologous graft	181/203 (89.2%)	161/201 (80.1%)	9.1 [2.1 ; 16.0]
Age of patients			
<16 years	27/39 (69.2%)	24/45 (53.3%)	
≥16 years	313/386 (81.1%)	312/412 (75.7%)	
>64 years	32/33	13/23	
Type of infection			
Proven	6 (1.4%)	8 (1.8%)	
Aspergillus spp.	0 (0.0%)	4 (0.9%)	
Candida spp.	4 (0.9%)	2 (0.4%)	
Fusarium spp.	1 (0.2%)	2 (0.4%)	
Zygomyces spp.	1 (0.2%)	0 (0.0%)	
Probable	1 (0.2%)	3 (0.7%)	
Aspergillus spp.	1 (0.2%)	3 (0.7%)	

*The 2 main reasons for exclusion from the *per protocol* population were no neutropenia below 200 cells/mm3 (criterion planned in the Statistical analysis plan).

The results of this study demonstrated that micafungin was superior[6] to fluconazole for the primary endpoint, the overall success rate, in the ITT population (80.0% versus 73.5%; p=0.03); though the degree of the effect was modest (difference of 6.5%; $CI_{95\%}$ [0.9; 12.0]).

Sub-group analyses performed according to the type of graft and the type of infection confirmed the non-inferiority compared to fluconazole, in particular regarding the prevention of *Candida* infections in allogeneic haematopoietic stem cell recipients[7]. Breakthrough infections by *Aspergillus* species were less frequent in the micafungin group than in the fluconazole group, which is consistent with the lack of activity of fluconazole against filamentous fungi (including *Aspergillus spp.*).

The frequency of use of a systemic antifungal treatment during the follow-up phase (59.5% versus 65.2%) and mortality rates (4.2% versus 5.7%) were similar in the two treatment groups.

3.2. Safety (clinical experience see SPC)

The safety profile of micafungin is based on data for 3,028 patients treated by micafungin during clinical trials.
The incidence of adverse effects was 28.1%. The most commonly reported adverse effects were nausea (2.8%), an elevation of blood alkaline phosphatase levels (2.7%), phlebitis (2.5%, mainly in HIV-infected patients with peripheral catheters), vomiting (2.5%) and an elevation of aspartate aminotransferase levels (2.3%).

Hepatic adverse effects (AE)
The incidence of hepatic AE in clinical trials was 8.6% (260/3028) of micafungin-treated patients. Most AE were of mild to moderate severity. The most frequent reactions were an increase in blood pressure (2.7%), ASAT (2.3%), ALAT (2.0%), bilirubinaemia (1.6%) and abnormal liver function test results (1.5%). The incidence of AE was higher with micafungin (11.4%) than with liposomal amphotericin B (6.4%) in the comparative study FG-463-21-08 performed in invasive candidiasis, but similar to that of fluconazole or caspofungin in the other clinical trials. Few patients (1.1%; 0.4% of serious cases) discontinued the treatment because of hepatic AE.
The incidence of hepatic AE (increase >2.5 ULN of ASAT, ALAT and bilirubinaemia) was approximately twice as high in children as in adults. Moreover, the frequency of increases in ALAT, ASAT and blood pressure in children <1 year was approximately twice as high as in older children.

[6] Superiority analysis planned in the protocol if non-inferiority was demonstrated
[7] Populations at high risk of invasive fungal infections and for whom chemoprophylaxis is justified are haematopoietic stem cell transplant (HSCT) recipients and patients treated for acute leukaemia.

Effects on renal function

The incidence of renal AE (mainly increases in creatinine and blood urea levels) was 1.7%.

In the treatment of invasive candidiasis, the incidence of renal AE was lower in the micafungin group than in the liposomal amphotericin B group (study FG-463-21-08) in the adult population (4.9% vs. 12%, including an increase in creatinine: 1.9 % vs. 6.4%); in the paediatric population, renal AE were reported in 4 (7.7%) patients in the micafungin group and 3 (5.6%) patients in the liposomal amphotericin B group [including an increase in blood urea: 2 (3.8%) vs. 1 (1.9%); renal failure: 2 (3.8%) vs. 1 (1.9%)]. In study 03-0-192 (micafungin 150 mg vs. caspofungin), the incidence of renal AE was 12.4% vs. 7.8% (including acute renal failure: 4.0% vs. 3.1%; worsened renal impairment 2.5% vs. 0.5%). In the other clinical trials, in particular in the context of oesophageal candidiasis and prophylaxis of Candida infections, the incidence of renal AE was lower and similar to that of caspofungin and fluconazole. Overall, few patients (4 patients including 2 serious cases) discontinued treatment because of renal AE. The incidence of renal AE was higher in children than in adults [3.7% vs. 1.4%; including acute renal failure (1.0% vs. 0.1%), increase in blood urea (1.7% vs. 0.5%)].

Special warnings and precautions for use concerning the risks of hepatic (major deterioration in hepatic function) and renal damage (renal failure and abnormal renal function tests) have been included in the SPC (cf. SPC).

The marketing of micafungin is conditioned by a risk management plan in order to control safety aspects and notably the risk of hepatic and renal damage. These additional pharmacovigilance measures include an observational study to evaluate the safety of IV micafungin in the treatment and prophylaxis of candidiasis in adults and children versus other IV antifungal agents. A study will be performed in young rats to better characterise the development of hepatic tumours.

3.3. Conclusion

Efficacy:

- *Candidaemia and invasive candidiasis: micafungin versus liposomal amphotericin B (Study FG-463-21-08) or caspofungin (Study 03-0-192).*

In study FG-463-21-08 performed in adult and paediatric patients, micafungin was not inferior (delta threshold = 15%) to liposomal amphotericin B regarding the treatment success rate (clinical and mycological response) observed in adult patients in the PP population (89.6% vs. 89.5%; difference + 0.1. $CI_{95\%}$ [-5.9 ; 6.1]). The number of paediatric patients was insufficient to permit comparative analysis with a sufficient statistical power (success rate in the PP population: 85.4 % [35/41] vs. 88.1 % [37/42]; difference - 2.7 [-17.3 ; 11.9]).

In study 03-0-192 performed in adult patients, micafungin was not inferior (delta threshold = 15%) to caspofungin (success rate: 82.3% in the micafungin 100 mg group versus 77.2% in the caspofungin group; difference + 5.2% [-3.3 ; 13.3]).

It should be noted that as only a very limited number of patients had invasive candidiasis or were neutropenic in these two studies, no conclusions can be drawn with respect to efficacy in these more severe forms.

- *Oesophageal candidiasis: IV micafungin, 150 mg/day versus IV fluconazole, 200 mg/day (Study 03-7-005)*

The results of study **03-7-005** showed the non-inferiority (delta threshold = 10%) of micafungin compared to IV fluconazole in adult HIV-seropositive patients primarily infected by *C. albicans (98% of cases).* Treatment success rates defined by an endoscopic score = 0 (disappearance of lesions, endoscopic cure) at the end of the treatment were, for the PP population, 96.8% in the micafungin group and 94.8% in the fluconazole group; difference + 2% [-2.0%, 6.0%]. The mycological eradication rate was 68.8% versus 73.3%.

- *Prophylaxis of Candida fungal infections in patients undergoing allogeneic haematopoietic stem cell transplantation: Micafungin versus fluconazole (Study 98-0-050)*

The results of **study 98-0-050** demonstrated a superiority of micafungin over fluconazole with respect to the overall success rate[8], (80.0% versus 73.5% in the ITT population, p=0.03); however, this effect was modest (difference 6.5%; CI $_{95\%}$ [0.9; 12.0])

Sub-group analyses performed according to the type of graft and the type of infection confirmed the **non-inferiority** compared to fluconazole, in particular in the prevention of ***Candida* infections** in **allogeneic[9]** haematopoietic stem cell recipients. Breakthrough infections by *Aspergillus* species were less frequent in the micafungin group (0.2%, 1 probable case) than in the fluconazole group (1.5%, 4 proven cases and 3 probable cases) which is consistent with the lack of activity of fluconazole against filamentous fungi (including Aspergillus spp.). A comparative study versus another antifungal agent with a spectrum identical or similar to that of micafungin (including filamentous fungi such as *Aspergillus spp.*), would have been more relevant.

Safety

The most commonly reported adverse effects during clinical trials were nausea, vomiting, phlebitis, elevated alkaline phosphatase levels and an increase in aspartate aminotransferase.
Special warnings and precautions for use concerning the risks of hepatic impairment (major deterioration in hepatic function) and renal damage (renal failure and abnormal renal function tests) have been included in the SPC (cf. SPC). The marketing authorisation of micafungin is conditioned by a risk management plan in order to control safety aspects.

[8] Primary efficacy endpoint: defined by the absence of proven, probable or suspected systemic fungal infection during treatment *and* during the 4-week follow-up period after treatment.
[9] Populations at high risk of invasive fungal infections and for whom chemoprophylaxis is justified are haematopoietic stem cell transplant (HSCT) recipients and patients treated for acute leukaemia.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The disorders concerned by these proprietary medicinal products are life-threatening immediately or as a result of complications The seriousness of infection by *Candida spp.* depends on the sites/organs affected and the underlying clinical context. Candidaemia has a high mortality, in particular in patients with cancer or haematological malignancies. Oesophageal candidiasis mainly occurs against a background of HIV infection and is one of the AIDS classifying disorders.

This medicinal product is intended to provide curative or preventive treatment.

The efficacy/safety ratio of these medicinal products is high, on condition of compliance with the special warnings and precautions for use (see SPC).

Alternative treatments are available, but in children are few in number.

Public health benefit (currently under validation)
Invasive candidiasis and oesophageal candidiasis are serious and life-threatening clinical conditions that constitute a moderate public health burden.

The improvement in the curative and preventive treatment of these *Candida* infections, in particular those resistant to existing treatments and certain very severe forms, is an important therapeutic need but does not constitute a public health priority. For children, the need for medicines suitable for paediatric use is a public health priority.

A review of the available clinical trial data (non-inferiority trials), shows that this proprietary medicinal product is not expected to have an additional impact in terms of morbidity and mortality in these patients. This is reinforced by the fact that these clinical trial results may not be transposable to real-life conditions because of:
- the small percentage in the trials of patients with invasive candidiasis or neutropenia and uncertainty about the resistance status of patients to a prior therapy,
- doubts about the safety profile of MYCAMINE,

Consequently, MYCAMINE is not expected to benefit public health in this indication.

The actual benefit is substantial in the indications and at the dosages of the MA.

4.2. Improvement in actual benefit

In adults:

MYCAMINE does not improve actual benefit (IAB V) compared to other drugs recommended for the curative treatment of candidaemia/invasive candidiasis and oesophageal candidiasis, or for the prophylaxis of infections by *Candida spp*.

It constitutes a useful additional means of treatment for the management of these infections, but its role in therapeutic strategy merits more detailed investigation.

In children:

MYCAMINE provides a minor improvement in actual benefit (IAB IV) in terms of efficacy in the management of candidaemia/invasive candidiasis and for the prophylaxis of Candida infections, in view of the relatively small number of therapeutic alternatives with a Marketing Authorisation in this population.

4.3. Therapeutic use

- Therapeutic strategy in systemic candidiasis[10]
  - Adults

The 2004 consensus conference recommended the use of amphotericin B for the treatment of systemic candidiasis in the absence of renal insufficiency (serum creatinine levels <1.5 times normal), or fluconazole except in patients with neutropenia or who have received prior fluconazole therapy. 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 susceptible to fluconazole, a switch to fluconazole is recommended, and if the strain is found to be resistant or to have dose-dependent susceptibility, treatment with amphotericin B, voriconazole, caspofungin or liposomal amphotericin B is prescribed.
Anidulafungin (ECALTA), which was not mentioned in the 2004 consensus conference, was granted a Marketing Authorisation (September 2007) in the treatment of invasive candidiasis in non-neutropenic adults[11]. It could claim the same indications as caspofungin. However, unlike caspofungin, anidulafungin does not have a Marketing Authorisation in the event of neutropenia. According to its in vitro spectrum of activity, it should have in vivo activity against non *albicans Candida spp*. However, few clinical efficacy data are available regarding *Candida albicans* infections resistant to fluconazole or *non-albicans Candida* (54 patients in study VER002-9).

Micafungin (MYCAMINE) could be positioned at the same level as caspofungin on the basis of demonstration of its clinical efficacy. However, in view of the reservations concerning its safety, and in accordance with the wording of the Marketing Authorisation, MYCAMINE should only be used when the administration of other antifungal agents is inappropriate.

  - In children

Fluconazole and amphotericin B remain the reference agents in children, in the absence of specific guidelines, and can be used at any age. Voriconazole (VFEND) has a Marketing Authorisation in children from the age of 2 years.
MYCAMINE is the first compound in the echinocandin family that can be used in children of all ages. It could constitute an alternative in children with candidaemia or invasive candidiasis, in the event of renal insufficiency and prior treatment with fluconazole, after taking account of the reservations relative to its safety. The number of children who cold be treated with MYCAMINE in France in this case seems quite limited (expert opinion).

- **Oesophageal candidiasis[12]**

The therapeutic strategy for oesophageal candidiasis in adults was defined in the Yeni report in 2008: “Oesophageal candidiasis requires first-line treatment by oral fluconazole at a dose of 200 mg on day 1, then 100 mg/day, which can be increased to 400 mg in the event of clinical failure. Itraconazole, 200 mg/day in capsules or solution, amphotericin B (0.3 to 0.6 mg/kg/day, with the liposomal form in the case of renal insufficiency) are the second-line treatments. Other antifungal agents, such as caspofungin (CANCIDAS), voriconazole (VFEND) or posaconazole (NOXAFIL), can be used in the event of clinical failure or according to the fungal susceptibility test data, though the first two do not have a Marketing Authorisation in this indication”.
The use of MYCAMINE cannot be envisaged as first-line therapy for oesophageal candidiasis because it must be administered via the intravenous route and in light of the reservations concerning its safety. It could constitute an alternative in patients who need to be treated intravenously (severe oesophagitis) and present with intolerance to fluconazole, or candidiasis caused by a fluconazole-resistant strain. Concerning this

[10] SFAR, SPILF, SRLF common consensus conference: Management of invasive aspergillosis and candidiasis in the adult. Elsevier SAS. 2004.
[11] Cf. Transparency Committee opinion (5 March 2008) concerning the product ECALTA (last medicinal product listed in this indication)

[12] 2008 Expert Group Report on the medical management of the patients infected by HIV, directed by Prof. Patrick Yeni. 19 August 2008

latter condition, it should be emphasised that the data available[13] do not definitely validate the use of MYCAMINE in this setting.

- **Prophylaxis of fungal infections**

According to the consensus conference (SFAR, SPILF, SRLF, 2004) on the chemoprophylaxis of fungal infections in haematology[14], "antifungal prophylaxis should only be administered to patients at very high risk of fungal infection, i.e. those in whom the expected benefit of antifungal prophylaxis a priori outweighs the risk of bacteraemia. This is because two broad prospective studies showed that the prophylactic administration of antifungal agents is significantly associated with a higher incidence of bacterial infections
The two populations at high risk of invasive fungal infections (IFI) are haematopoietic stem cell transplant (HSCT) recipients and patients treated for acute leukaemia (AML). IFI, and in particular aspergillosis, is the leading infectious cause of death after transplantation. Drug prophylaxis is only one of the strategies to reduce the incidence of IFI in high-risk patients.
Candidate compounds are the azole compounds (fluconazole, itraconazole, voriconazole), polyenes (amphotericin B) and echinocandins. Only major prospective trials will accurately determine the prophylactic value of certain antifungal agents.
Neither fluconazole, nor itraconazole significantly prevent IFI during AML.
Fluconazole reduces mortality by IFI in HSCT recipients,. The results of these studies are however open to question following the epidemiological changes observed in Candida infections.
Itraconazole reduces IFI without reducing overall mortality and causes problems of drug interference and hepatic toxicity leading to its discontinuation in more than one third of cases.
None of the trials carried out with polyenes gave conclusive findings. There is currently no available prospective study on voriconazole"

In practice, posaconazole (NOXAFIL), which was not mentioned in the 2004 consensus conference (October 2006), constitutes one of the first-line treatments for oral administration[15] in allogeneic haematopoietic stem cell transplant recipients (HSCT) or patients treated for acute leukaemia and who are at high-risk of fungal infection[16].

Role of MYCAMINE

The epidemiology of invasive fungal infections has changed in recent years with a lower incidence of candidiasis and an increased frequency of invasive aspergillosis, fusariosis and zygomycosis. This evolution is partly due to the preventive treatment regimens used during recent years (fluconazole in particular). This evolution is particularly marked for allograft recipients with major and prolonged neutropenia, in whom antifungal prophylaxis has been shown to be useful. No formal or definitive conclusions can be drawn at present because of the lack of recent French consensus on this point. The best choice probably involves the use of compounds with proven efficacy in the prevention and treatment of candidiasis and invasive aspergillosis (itraconazole, posaconazole), which is not the case for micafungin according to the current application. Moreover, at equivalent efficacy, the availability of an oral form is an advantage for prophylactic treatment that may be prolonged. In addition, insufficient data are available on micafungin concerning the risk of breakthrough infections (for example due to *Trichosporon spp.*) and/or the risk of selection of strains presenting cross-resistance with other therapeutically useful compounds (other echinocandins, in particular).

Thus the role of MYCAMINE in the primary prophylaxis of *Candida* infections in adults and children is restricted by the constraint that it requires IV administration, the lack of evidence concerning its *in vivo* curative efficacy against *Aspergillus* in particular (important information, from the point of view of clinical practice), and reservations about the safety and ecological impact of this prophylaxis.

[13] Adult HIV-seropositive adults, mainly infected by *C. albicans*
[14] Cordonnier C., Pautas C., Maury S., Kuentz M. Chemoprophylaxis of fungal infections in haematology. SFAR, SPILF, SRLF common consensus conference: Available online at www.sciencedirect.com
[15] Cf. Transparency Committee opinion (18 July 2007) concerning the proprietary medicine NOXAFIL.
[16] Main risk factors: duration of neutropenia ≤ 500 neutrophils (low risk ≤ 5 days, intermediate risk 6-9 days, high risk ≥ 10 days) but also neutropenia-inducing conditioning regimen, GVH, prolonged corticosteroid therapy.

4.4. Target Population

- Candidaemia/invasive candidiasis

The target population for MYCAMINE corresponds to adult patients and children with candidaemia or invasive candidiasis in whom the administration of other antifungal agents is inappropriate.

The incidence of candidaemia can be evaluated to be between 0.20 and 0.29 cases per 1000 admissions[17,18].

The number of hospital stays (full hospitalisation) in Medicine, Surgery and Obstetrics (MCO) departments in 2006 in private and public hospitals was 10,238,000[19]..

If these two parameters are multiplied together an estimation of the annual number of cases of candidaemia of about 2000 – 3000 is obtained. However, the target population for MYCAMINE is probably smaller as this treatment is reserved for those patients in whom the administration of other antifungals is inappropriate.

- Oesophageal candidiasis

Oesophageal candidiasis mainly occurs against a background of HIV infection. The incidence of oesophageal candidiasis has decreased considerably since highly active antiretroviral medications have become available which restore immune function (even only partially). During the first half of 2006, 104 cases of oesophageal candidiasis were recorded in the French Hospital Database for HIV infection (FHDH)[20]. Assuming that the incidence remained stable during the two six-month periods, this gives a total of 208 cases of oesophageal candidiasis among patients followed up in the FHDH database in 2006. Considering that 50 to 60% of reimbursed HIV-positive individuals are included in this database[21], the annual number of patients infected by HIV who develop oesophageal candidiasis can be estimated to be 350 to 400.

In practice, the target population for MYCAMINE is represented by patients who must be treated intravenously (severe oesophagitis) and present with intolerance to fluconazole, or candidiasis caused by a fluconazole-resistant strain.
Recurrence or occurrence in patients receiving antiretroviral medication have become exceptional and suggest problems of compliance with treatment rather than the microbiological failure of first-line antifungal medication (fluconazole).

It can therefore be estimated that MYCAMINE could be proposed in fewer than about thirty cases of oesophageal candidiasis per year in France (expert opinion).

- Prophylaxis of fungal infections by *Candida spp*.

Populations at a high risk of invasive fungal infections and for whom chemoprophylaxis is justified are haematopoietic stem cell (HSC) transplant recipients and patients treated for acute leukaemia.

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[17] Tortorono 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 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

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

[19] DREES.The activity of health institutions in 2006 for full and partial hospitalisation . N°618. December 2007 Available at http://www.sae-diffusion.sante.gouv.fr(viewed on 03/11/2008).

[20] INSERM Feedback of clinical and epidemiological data. Inserm U 720. September 2007.n°15. http://www.ccde.fr/_fold/fl-1197641440-907.pdf (viewed on 3/11/2008).

[21] Bernillon P, Lievre L, Pillonel J, Laporte A, Costagliola D. Record-linkage between two anonymous databases for a capture-recapture estimation of underreporting of AIDS cases: France 1990-1993. The Clinical Epidemiology Group from French Human Immunodeficiency Virus Information and Care Centres. Int J Epidemiol 2000;29(1):168-74.

- In 2000, there were an estimated total number of 6,243 new cases of leukaemia Acute forms accounted for 41.5% of cases (incidence rates of 4.3 per 100,000 in men and 3.2 per 100,000 in women), i.e. approximately 2,600 cases per year. The average age was approximately 60 years[22].
- In 2007 1,351 patients received 1,379 allogeneic HSC grafts[23]. The proportion of paediatric cases (age below 18 years) was 21.1% of allografts.

Hence, the number of patients eligible for the prophylactic treatment of invasive fungal infections (candidiasis, aspergillosis) is approximately 4000 to 5000 per year[24].

In practice, a smaller number of patients would probably receive MYCAMINE as this treatment is reserved for the prophylaxis of infections by *Candida spp.* in particular in the absence of alternative treatments.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicin approved for use in hospitals and various public services in the indications and dosages of the MA.
The Committee notes that the Marketing Authorisation for micafungin is conditioned by a risk management plan in order to control safety aspects.

[22] Guizard AV, Carli PM, Troussard X. Evaluation de l'incidence et de la mortalité par cancer entre 1978 et 2000. http://www.invs.sante.fr/publications/2003/rapport_cancer_2003/p175_toutes_leucemies.pdf
[23] Biomedecine Agency: Assessment of graft harvesting and transplantation activities in France in 2007.
[24] Cf. Transparency Committee opinion (18 July 2007) concerning the proprietary medicine NOXAFIL.