All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Micafungin (Mycamine®▼) for the treatment of invasive candidiasis in adults and children

Astellas Pharma Ltd

Advice No: 0309 – February 2009

Recommendation of AWMSG

Micafungin (Mycamine®▼) is not recommended for use within NHS Wales for the treatment of invasive candidiasis in adults (including the elderly) and children (including neonates).

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 25th February 2009

The recommendation of AWMSG is:

Micafungin (Mycamine®▼) is not recommended for use within NHS Wales for the treatment of invasive candidiasis in adults (including the elderly) and children (including neonates).

Key factors influencing the recommendation:

The case for cost effectiveness of micafungin (Mycamine®▼) has not been proven.

Additional notes:

The holder of the marketing authorisation has not made a submission to AWMSG for the appraisal of micafungin (Mycamine®▼) for its other licensed indications:

- Prophylaxis of Candida infection in adults (including the elderly) and children (including neonates) undergoing allogeneic haematopoietic stem cell transplantation (SCT) or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / microL) for 10 or more days

- Treatment of oesophageal candidiasis in adults aged 16 years and over (including the elderly) for whom intravenous therapy is appropriate.

As a result, AWMSG cannot provide advice in relation to these two indications.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Micafungin (Mycamine®▼) is indicated for:

- Treatment of invasive candidiasis in adults (including the elderly) and children (including neonates)
- Prophylaxis of Candida infection in adults (including the elderly) and children (including neonates) undergoing allogeneic haematopoietic stem cell transplantation (SCT) or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells / microL) for 10 or more days
- Treatment of oesophageal candidiasis in adults aged 16 years and over (including the elderly) for whom intravenous therapy is appropriate.

The decision to use micafungin should take into account a potential risk for the development of liver tumours. Micafungin should therefore only be used if other antifungals are not appropriate[1].

2.2 Dosing

Consideration should be given to official/national guidance on the appropriate use of antifungal agents. Treatment with micafungin 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 the 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[1].

Micafungin should be administered by intravenous (IV) infusion over approximately one hour. The dose regimen depends on the body weight of the patient and the indication. In the treatment of invasive candidiasis a dose of 100mg/day in patients weighing >40kg, and a dose of 2mg/kg/day in patients weighing ≤40kg is recommended. If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200mg/day in patients weighing >40kg or 4mg/kg/day in patients weighing ≤40kg. *Candida* infection should be treated for 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[1].

See the micafungin Summary of Product Characteristics (SPC) for full details and the dosing information for its other licensed indications[1].

2.3 Market authorisation date

25th April 2008[2].

2.4 UK Launch date

1st August 2008[2].

3.0 DECISION CONTEXT

Invasive fungal infections are a frequent cause of morbidity and mortality in high risk patients[5] and are increasing in frequency in all western countries. This is due to a variety of factors, including an increase in intensive care given to critically ill patients, the use of invasive technologies and indwelling intravascular catheters, and the use of broad-spectrum antibiotics[3]. *Candida* species are one of the leading causes of nosocomial blood stream infections (candidaemia)[3]. *C. albicans* is the predominant species but non-albicans species (e.g. *C. glabrata*, *C. krusei*) are increasingly associated with invasive candidiasis[4]. The shift in the epidemiology of *Candida* infections, and the increasing emergence of resistant strains, has important clinical and therapeutic implications[3].

Several antifungal agents are available for the treatment of invasive candidiasis, but their indications differ[3,4,6]. Fluconazole (IV and/or oral routes) is an option for *C. albicans* infection in clinically stable patients who have not recently received an azole antifungal[6]. However, fluconazole-resistant *Candida* strains have emerged (e.g. *C. krusei* and *C. glabrata*)[3,4]. Amphotericin B can be given by IV infusion against virtually all strains of *Candida albicans*; but there are increasing concerns about its activity against other *Candida* species[3]. There are issues of renal toxicity with the conventional amphotericin B formulation (Fungizone®), and alternative lipid-based preparations (Abelcet®, AmBisome®, Amphocil®), which may reduce this risk, are significantly more expensive than the conventional amphotericin formulation. Voriconazole (IV or oral) can be used for infections caused by fluconazole-resistant *Candida* species that have not responded to amphotericin, or in patients intolerant of amphotericin[6]. In refractory cases, IV flucytosine can be used in combination with amphotericin[6].

Micafungin belongs to the echinocandin class of antifungal agents, which exert their effect by inhibiting fungal cell wall synthesis. This is a different mode of action to other classes of agents such as the azoles, which interfere with the cell wall structure itself[5]; therefore, cross-resistance with other antifungal classes is not expected. Furthermore, in contrast to the azoles, micafungin has a low potential for interaction with other drugs that are metabolised via CYP450 pathways[5]. Two other echinocandins are currently licensed. Like micafungin[1], caspofungin (Cancidas®) is licensed for use in adult or paediatric patients, and in the treatment of invasive candidiasis this is irrespective of neutropenic status[7]. Anidulafungin (Ecalta®▼) is licensed for use only in non-neutropenic adult patients[8].

In reaching its recommendation for the granting of a marketing authorisation for micafungin, the Committee for Human Medicinal products (CHMP) concluded that, due to a potential risk for the development of liver tumours, the benefit/risk ratio of all other antifungals is "superior" to micafungin in "uncomplicated" clinical situations (e.g. absence of: resistant strain, multiple co-medication, renal insufficiency). In other cases micafungin might be an adequate treatment option in life threatening situations despite this potential risk. The overall benefit/risk of micafungin is positive and can be recommended as a treatment option only when the use of other antifungals is not appropriate[5].

The company has restricted the micafungin submission to the treatment of invasive candidiasis in adults and children[2]. No case is made for the use of micafungin as prophylaxis against *Candida* infection, nor in the treatment of oesophageal candidiasis.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Phase III trials have demonstrated that micafungin is non-inferior to caspofungin (Cancidas®) and a liposomal amphotericin B (L-AmB) preparation (AmBisome®) in the treatment of invasive candidiasis in adults over a median of 14-15 days. A sub-study of the trial against L-AmB suggested similar efficacy in paediatric patients, but this trial was not powered for statistical comparisons. Micafungin appeared to be equally effective in the treatment of invasive candidiasis due to *C. albicans* and non-albicans strains. The adverse event profile of micafungin is similar to caspofungin. Compared with L-AmB, micafungin was associated with a numerically, but not statistically significantly lower overall incidence of serious treatment-related adverse events and discontinuations due to adverse events. Discontinuations due to renal events and infusion-related reactions were more common with L-AmB, whereas discontinuations due to hepatic events were more common with micafungin. Careful monitoring of liver function, with early discontinuation in the presence of significant and persistent elevation of liver enzymes, is recommended.

4.2 Review of the evidence on cost-effectiveness

The company submission describes separate cost effectiveness analyses of micafungin compared with L-AmB and caspofungin in adult patients. These are based on a simple decision analytic model that is populated with patient-level efficacy data from two phase III studies of micafungin. The outcome measure for these analyses is the percentage of patients successfully treated and alive at the end of follow-up. No economic evidence specifically in children is presented, and the analyses do not specifically represent a situation where micafungin is being used because the use of other antifungals is not appropriate, as is stipulated in the licensed indication for micafungin. There are several limitations in the methods employed, including the selection of a short time horizon of analysis where there is differential impact on mortality; assumptions around patients who were lost to follow-up; and lack of consideration of health-related quality of life.

In the base case analyses the models predict that micafungin is less expensive and more effective than both L-AmB and caspofungin. For the L-AmB comparison, no specific sensitivity analyses are presented beyond a probabilistic sensitivity analysis, which limits interpretation of the results. For the caspofungin comparison, several scenario analyses are presented, which indicate that the model is relatively insensitive to several assumptions. In addition, the results are similar in several sub-groups, including patients with APACHE II scores $\leq$20 or >20, patients aged 18-64 years or 65 years and older, and in patients with *C. albicans* or non-albicans infection. However, the model was sensitive to the assumptions made around time spent on intensive care units and general wards, and scenario analyses conducted for the comparison with caspofungin yielded positive incremental cost-effectiveness ratios.

5.0 LIMITATIONS OF DECISION CONTEXT

- Most data are from adult patients with invasive candidiasis confined to the blood stream. Data in patients with non-candidiaemic invasive candidiasis are limited.
- Most adult patients had APACHE II scores $\leq$20 and few patients were neutropenic. It is likely that many patients in clinical practice will be more severely ill and at higher risk of complications than those included in the micafungin trials.

- The economic evidence presented does not specifically relate to the licensed indication for the use of micafungin when the use of other antifungals are not appropriate.

6.0 CLINICAL EVIDENCE

The company submission[2] provides details of two phase III, randomised, double-blind, non-inferiority studies of micafungin against caspofungin[9] and liposomal amphotericin B (L-AmB)[10] in adult patients with candidaemia or invasive candidiasis. The former study included a micafungin arm with an initial dose of 150mg/day[9], which is not discussed in detail here as the recommended initial dose in invasive candidiasis is 100mg/day[1]. The latter study involved a sub-study in neonates and children aged 16 years or younger, the results of which are discussed but are descriptive only; this sub-study was not powered for statistical comparisons[11].

The primary endpoint in these studies was investigator-defined treatment success. Treatment success is defined as those achieving both clinical and mycological success, with clinical success defined as complete response (resolution of all attributable signs, symptoms, and abnormal radiographic findings associated with fungal infection) or partial response (improvement of attributable signs, symptoms, and abnormal radiographic findings since baseline), and mycological success defined as eradication of infection for patients with candidaemia or presumed eradication of infection for patients with non-candidaemic invasive candidiasis.

Details and summary results are presented in Table 1A, Appendix 1 and are discussed below.

6.1 Clinical efficacy

6.1.1 Phase III trial of micafungin compared with caspofungin

In this trial, adults (≥18 years) with at least one positive blood culture for *Candida* (candidaemia), or a diagnosis of noncandidaemic invasive candidiasis (including a *Candida*-positive culture from a normally sterile site other than the blood stream), were randomised to treatment with micafungin 100mg or caspofungin (70mg on day one, followed by 50mg thereafter), administered once daily by IV infusion for 14 to 28 days. Investigators were encouraged to continue treatment for 14 days after clearance of *Candida* from the blood stream and resolution of symptoms. A switch to oral fluconazole was permitted after at least 10 days of blinded IV therapy[9].

Median duration of overall antifungal therapy was 14 days and around 21% of patients in each group were switched to oral fluconazole treatment at the end of blinded IV therapy. The primary endpoint of investigator-defined treatment success at the end of blinded IV treatment, assessed in the modified intention to treat (mITT) population, was met by 76.4% of the micafungin group and 72.3% of the caspofungin group (difference 4.1%; 95% confidence interval [CI] -4.4% to 12.3%). As the lower limit of the CI was greater than -15%, micafungin was declared to be non-inferior to caspofungin. In those patients in whom treatment was successful, similar proportions had *C. albicans* and non-albicans species at baseline. Although there were some subtle numerical differences, there were no statistically significant differences between treatments in the rates of treatment success for any particular baseline characteristic that was considered. However, the number of patients with some characteristics was small (e.g. only eight patients in the micafungin and four in the caspofungin groups had *C. krusei* isolated at baseline). There was no significant difference in the time to achieve negative blood cultures or mycological eradication[9].

Overall, treatment success rates declined in both the micafungin and the caspofungin group when assessed at the end of all antifungal therapy (74.9% versus 70.2%), two weeks later (54.5% versus 50.5%), and at six weeks later (46.6% versus 42.6%). Overall relapse rates were similar at around 20%, and around 15% of each group received empirical therapy or treatment with antifungal medication during the post-treatment follow up[9].

Points to note:

- The mean age of patients was 56 years, around 85% had candidaemia only (i.e. 15% had invasive candidiasis without candidaemia), around 91% did not have neutropenia at baseline and around 81% had APACHE II scores $\leq$20[9]. Most patients in this trial may therefore have been less severely ill or at lower risk of morbidity or mortality than many patients in practice.
- Treatment success rates in both treatment arms were numerically lower in patients with APACHE II scores >20 (60.0% with micafungin, 58.3% with caspofungin) compared with those with scores $\leq$20 (80.1% and 75.7%, respectively). However, these results should be interpreted with caution as the trial was not designed for these comparisons.
- A blinded data review panel comprising of five infectious disease physicians confirmed baseline diagnoses and investigators' assessments of clinical and mycological outcomes. Concordance in the diagnoses of candidaemia at baseline was 96.9%. In the assessment of the primary endpoint, the data review panel estimates of treatment success were 72.8% for micafungin and 70.7% for caspofungin (compared with 76.4% and 72.3%, respectively, for the investigators' estimates); concordance with the investigators' assessments was 92.2%[9].
- The definition of clinical success included complete and partial responses to treatment. In both treatment groups, complete response rates were lower in patients with invasive candidiasis compared with patients with candidaemia (i.e. a greater proportion of the clinical success achieved in patients with invasive candidiasis was attributed to partial response than in patients with candidaemia) (see Table 1A, Appendix 1).
- In those who switched to oral fluconazole, the median duration was 7.5 days in the micafungin group and 4 days in the caspofungin group.
- Two-thirds of patients had an intravascular catheter in place at baseline. There were no significant differences in treatment success rates between groups in patients in whom the catheter was removed/replaced.
- More patients died in the micafungin group (29%) than the caspofungin group (26.4%) but there was no significant difference in survival and no deaths were attributed to study drugs[9].

6.1.2 Phase III trial of micafungin compared with L-AmB

In this trial, patients aged 16 years and over, with clinical signs of systemic candida infection and at least one positive culture for *Candida*, were randomised to treatment with micafungin 100mg or L-AmB (Ambisome®) 3mg/kg, administered once daily by IV infusion for 14 to 28 days (or up to 56 days for some specific conditions). Doses were fixed for the first five days, after which it could be increased if infection was persistent[10].

In the per-protocol population, the median duration of overall antifungal therapy was 15 days in both treatment groups. The primary endpoint of investigator-defined treatment success at the end of treatment, assessed in the per-protocol population, was met by 89.6% of the micafungin group and 89.5% of the L-AmB group (difference 0.1%; 95%

CI -5.9% to 6.2%), indicating non-inferiority of micafungin to L-AmB. This was confirmed in the mITT analysis (74.1% versus 69.6%; difference 4.5%; 95% CI -3.5% to 12.4%)[10].

In the per-protocol population, there was little difference in treatment success in patients with *C.albicans* (88.4% with micafungin versus 89.3% with L-AmB) and non-albicans species (89.7% versus 89.3%, respectively) at baseline. There was no significant difference in median time to first negative culture for patients with candidaemia (three days with micafungin versus four days with L-AmB). Mycological persistence at the end of treatment was the same in each group (9%) and recurrent infection during the 12 weeks of follow-up post treatment was similar (seven patients in the micafungin group and six in the L-AmB group). A proven emergent candida infection (i.e. an infection caused by a *Candida* species other than that recorded at baseline) was seen in one patient in the micafungin group and two patients in L-AmB group during the treatment phase and in three in the micafungin group and four in the L-AmB group during follow-up[10].

Points to note:

- The mean age of patients was 55 years, around 85% had candidaemia only (i.e. 15% had invasive candidiasis without candidaemia), around 88% did not have neutropenia at baseline and around 74% had APACHE II scores $\leq$20[10]. Most patients in this trial may therefore have been less severely ill or at lower risk of morbidity or mortality than many patients in practice.
- A blinded data review panel confirmed baseline diagnosis and investigator's assessment of clinical and mycological outcomes. Concordance in the diagnoses at baseline was 94.7% in the ITT population. In the assessment of the primary endpoint for the per-protocol population, the data review panel estimates of treatment success were 81.4% for micafungin and 80.4% for L-AmB[10].
- Patients were followed for 12 weeks post treatment, but overall treatment success rates are not presented over time.
- Based on the ITT population (n=531), during the entire treatment and 12-week follow-up periods, 40% of patients in each of the micafungin and L-AmB groups died. The fungal infection was considered by the investigator to have contributed to the cause of death for 34 (13%) patients in the micafungin group and 25 (9%) patients in the liposomal amphotericin B group (p=0.22)[10].

6.1.3 Sub-study of micafungin compared with L-AmB in paediatric patients

A paediatric sub-study was conducted alongside the phase III trial discussed in section 6.1.2[11]. This included neonates and children under 16 years of age. As in the above trial, most patients had candidaemia and were non-neutropenic. Overall treatment success in the mITT population was 72.9% for micafungin versus 76.0% for L-AmB. Treatment success was lower in both groups for patients with non-candidaemic invasive candidiasis than for patients with candidaemia. Treatment success was numerically higher with micafungin in neutropenic patients compared with non-neutropenic patients, whereas with L-AmB, treatment success was similar in both neutropenic and non-neutropenic patients (see Table 1A, Appendix 1). This study was not powered to provide statistical comparisons[11], and these results should be interpreted with caution.

6.2 Safety

In the study that compared micafungin against caspofungin[9], overall treatment-related adverse events were similar between the two groups (22.0% versus 23.8%, respectively)[9]. These included an increased serum alkaline phosphatase level,

abnormal results of liver function tests (LFTs), nausea, constipation, hypokalaemia, and rash. The number of adverse events of special interest (hepatic, renal, injection site reactions, histamine and/or allergic-type reactions, infusion-related reactions, and haemolysis) was reportedly similar across all groups, although few details are provided. Discontinuations due to adverse events were similar in those who received micafungin and those who received caspofungin (2.5% versus 3.6%, respectively) and there were no deaths attributed to study drugs[9].

In the study that compared micafungin against L-AmB in adults[10], the overall treatment-related adverse event rates were numerically lower with micafungin (43.2% versus 50.9%, respectively; p=0.082). Those that were significantly lower (p<0.05) included; rigors (0.8% versus 6.4%), back pain (0.4% versus 4.5%), infusion-related reaction (17.0% versus 28.8%) and increased blood creatinine (1.9% versus 6.4%). The mean peak decrease from baseline in estimated glomerular filtration rate was also significantly smaller in the micafungin group than in the L-AmB group (by -17.6mL/min/1.73m^2; 95% CI -24.1 to -11.1; p<0.0001). Serious treatment-related adverse events (4.2% versus 7.5%) and discontinuations due to adverse events (4.9% versus 9.0%) were numerically, but not statistically significantly lower for micafungin treatment. Discontinuations due to renal events (one patient in the micafungin group versus eight patients in the L-AmB group) and infusion-related reactions (one patient versus nine, respectively) were more common with L-AmB; whereas discontinuations due to hepatic events (seven patients versus three, respectively) were more common with micafungin[10].

The Scientific Discussion in the European Public Assessment Report (EPAR) notes that, overall, the nature and incidence of adverse events, irrespective of causality, were similar between paediatric and adult patients. However, there are some exceptions, including a doubling in the frequency of increases in liver transaminases and bilirubin to over 2.5 times the upper limit of normal compared with adults. In addition, children below 1 year of age experienced treatment-related increase in LFTs twice as often as older children. The most likely reason for these variations were different underlying conditions compared with adults or older paediatric patients observed in clinical studies[5].

The SPC states that the decision to use micafungin should take into account a potential risk for the development of liver tumours[1]. This is based on animal study data, but the EPAR states that the relevance of this finding for the therapeutic use in patients cannot be excluded. Liver function should be carefully monitored during micafungin treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of liver transaminases is recommended[1,5].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Several agents are indicated for the treatment of invasive candidiasis as discussed in section 3.0. Caspofungin and L-AmB are appropriate reference agents for determination of the comparative efficacy and safety of micafungin. However, the licensed indication for micafungin states that it should be used only if other antifungals are not appropriate[1].

7.2 Comparative effectiveness

- Micafungin has been shown in clinical trials to be non-inferior to caspofungin[9] and L-AmB[10] in the treatment of invasive candidiasis. The vast majority of patients in these trials had candidaemia rather than invasive candidiasis extending beyond the blood stream, were non-neutropenic and had APACHE II scores ≤20[9,10]. Therefore, the treatment success rates in clinical practice, where patients may be more severely ill and at greater risk of morbidity and mortality, may be lower than those observed in these trials. The fact that micafungin is only licensed for use when other antifungals are not appropriate[1] may also lead to different treatment success rates in clinical practice.
- Micafungin is licensed for the treatment of invasive candidiasis in patients of all ages, including neonates, and irrespective of neutropenic status[1]. Conventional amphotericin B (Fungizone®[12]), L-AmB (AmBisome®[13], Abelcet®[14] and Amphocil®[15]), fluconazole[16], and caspofungin[7] are similarly licensed for use in paediatric patients, and voriconazole is licensed for use in children aged two years and over[17]. Anidulafungin is only licensed for use in non-neutropenic adults[8].
- Micafungin has a low potential for interaction with other drugs that are metabolised via CYP450 pathways[1], and does not require dose adjustment for patients with renal impairment or mild-to-moderate hepatic impairment. In contrast, fluconazole and voriconazole have potential for many drug interactions due to CYP450 effects and both require dose adjustment for patients with renal impairment (but not oral voriconazole)[16,17]. The maintenance dose of voriconazole should be halved in the presence of mild-to-moderate chronic cirrhosis, but no adjustment for fluconazole or voriconazole are required in acute elevations in LFTs[16,17].
- Micafungin, as with the other echinocandins[7,8] and L-AmBs[13-15], is only available as an IV formulation[1]. This necessitates switching treatment class if/when moving patients from IV to oral therapy. Fluconazole and voriconazole are available as IV and oral formulations[16,17].
- Micafungin appears to be equally effective in the treatment of invasive candidiasis due to *C. albicans* and non-albicans strains[9,10] but clinical efficacy data in specific individual non-albicans strains are rather limited due to the small numbers of cases included in the trials.
- The echinocandins have a different mode of action to other classes of antifungals. Micafungin is fungicidal against *Candida* species, in contrast to fluconazole which is fungistatic[5]. The EPAR notes that neither cross-resistance with other antifungal classes, nor rapid development of resistance in fungal strains is expected with micafungin[5]. The micafungin SPC states that, as for all antimicrobial agents, cases of reduced susceptibility and resistance have been reported, and cross-resistance with other echinocandins cannot be excluded[1]. Most *Candida* and *Aspergillus* species are commonly susceptible to micafungin. Inherently resistant organisms include *Cryptococcus* species and *Fusarium* species (see the SPC for further details)[1].
- The adverse event profile of micafungin is similar to caspofungin. Compared with L-AmB, micafungin was associated with a numerically, but not statistically significantly lower overall incidence of serious treatment-related adverse events and discontinuations due to adverse events. Discontinuations due to hepatic events were more common with micafungin, whereas discontinuations due to renal events and infusion-related reactions were more common with L-AmB[10]. Due to a risk of infusion-related reactions, a test dose prior to initiating treatment with amphotericin-type antifungals is required[12-15]. The EPAR highlights a potential risk for the development of liver tumours with micafungin treatment, based on extended treatment in rodents. In reaching its

recommendation for the granting of a marketing authorisation, the Committee for Human Medicinal products (CHMP) concluded that micafungin would be approvable as a first-line treatment option for the claimed indications in all age groups if the risk for hepatocarcinogenicity could be excluded. As this risk, however, cannot be excluded for the time being, the benefit/risk ratio of all other antifungals is "superior" in "uncomplicated" clinical situations (e.g. absence of: resistant strain, multiple co-medication, renal insufficiency). In other cases micafungin might be an adequate treatment option in life threatening situations despite this potential risk. The overall benefit/risk of micafungin is positive and can be recommended as a treatment option only when the use of other antifungals is not appropriate[5].

- The company submission notes that no liver tumours have been observed during the clinical development programme or reported since marketing of the drug in several countries[2]. Post-marketing data (mostly from Japan), presented in the EPAR, indicates that 25% of adverse event reports have related to hepatic adverse events, some of which were fatal[5]. Careful monitoring of liver function, with early discontinuation in the presence of significant and persistent elevation of liver enzymes, is recommended[1].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for NMG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by micafungin (Mycamine®▼) over the relevant comparator(s), justify any additional costs and, if so, whether the total budgetary impact of supporting the use of micafungin (Mycamine®▼) is acceptable. The economic evidence presented in the company submission is restricted to the treatment of invasive candidiasis in adults; no evidence has been submitted in support of the other licensed indications[2].

8.2 Description and critique of the company's submission

The company submission describes two separate cost effectiveness analyses of micafungin compared with L-AmB and caspofungin, which are based on a simple decision analytic model[2]. These are populated with efficacy data from the two phase III studies of micafungin conducted in adult patients, as discussed in section 6[9,10]. No economic evidence specifically in children is presented, and the analyses do not specifically represent a situation where micafungin is being used because the use of other antifungals is not appropriate.

The outcome measure for these analyses is the percentage of patients successfully treated and alive at the end of follow-up, which differs from the primary endpoint of the two trials. No utility weights have been used in the analyses to adjust survival for health-related quality of life. For the analysis of micafungin compared with L-AmB, the efficacy data are taken from a sub-population of European and Australian patients, rather than the whole trial population, as was the approach in a published cost effectiveness analysis conducted from a German hospital perspective[18] and a UK adaptation recently presented as a conference poster[19]. This is not further explored in the submission. Resource use data are reportedly based on patient-level data taken from the same phase III trials. However, for the caspofungin comparison, assumptions have been made regarding the length of treatment in intensive care and on a general ward, and sensitivity analyses indicate that the model is sensitive to these assumptions. For the L-AmB comparison, no specific sensitivity analyses beyond the probabilistic sensitivity analysis have been conducted.

8.3 Population

Both analyses relate to adult patients only, as in the phase III trials discussed in section 6[9,10]. The vast majority of patients in these trials had candidaemia rather than invasive candidiasis extending beyond the blood stream, were non-neutropenic and had APACHE II scores <20[9,10]. It is feasible that many patients in clinical practice will be more severely ill and at higher risk of morbidity and mortality than most patients included in these trials. It should be noted that patients in these trials did not receive micafungin because the use of other antifungals was not appropriate (see section 8.5).

8.4 Perspective and time horizon

The analyses are conducted from a UK hospital perspective[2].

For the comparison of micafungin and L-AmB, a time horizon of 14 to 20 weeks is considered[2], based on the relevant phase III trial (initial treatment for two to eight weeks and a follow-up period after treatment of 12 weeks)[10].

For the comparison of micafungin and caspofungin, a time horizon of eight to 14 weeks is considered[2], as this is the time frame of the relevant phase III trial (initial treatment for two to eight weeks and a follow-up period after treatment of six weeks)[9].

As the treatments had a differential impact on survival, a lifetime horizon of analysis would be appropriate; however, it is acknowledged that this would present difficulties given the severe underlying conditions and co-morbitities of the patient population.

8.5 Comparator

Micafungin is compared against L-AmB and caspofungin in the economic analyses[2]. These would seem appropriate comparators for determining relative efficacy and safety, as per the clinical trials discussed in section 6[9,10]. The licensed indication states that micafungin should be used only if the use of other antifungals is not appropriate[1]. This stipulation is based on safety considerations (see sections 6.2 and 7.2). The clinical trials, and consequently the economic analyses, do not reflect the use of micafungin in such circumstances.

8.6 Clinical inputs

8.6.1 Efficacy data

The outcome measure for these analyses is the percentage of patients judged as successfully treated and alive at the end of follow-up. The definitions of treatment success are discussed in sections 6 and 7.2. This differs from the primary endpoint used in the clinical trials (see section 6), and the company submission states this allows analysis of relevant costs incurred after the initial treatment period[2]. Patient-level data have reportedly been used to determine this outcome.

L-AmB comparison

Only data relating to mITT population of European and Australian patients is included in the analysis. The company submission suggests that these patients approximate more closely those patients in Wales. However, no further exploration of the use of the whole study population is provided. The data for this analysis is presented in a published cost effectiveness analysis conducted from a German hospital perspective[18]. The data presented therein indicate that, of 93 European and Australian patients who received micafungin, 66 were successfully treated, of which 38 were alive and 13 were dead at the end of the follow-up period, and the remaining 15 were lost to follow-up. Of 84 European and Australian patients who received L-AmB, 57 were treated successfully, of which 34 were alive and 13 were dead at the end of the follow-up period, and the remaining 10 patients were lost to follow-up. In the base case analysis,

it is assumed that the probability of being alive at the end of the follow-up period for the drop outs is the same as for those who did not drop out. Therefore, for the micafungin drop-outs, it is assumed that 75% (i.e. 38/(38+13)) are alive at the end of the follow up period, compared with 72% (i.e. 34/(34+13)) for L-AmB drop-outs[2,18]. The overall effectiveness outcomes in the model are therefore 52.9% for micafungin and 49.1% for L-AmB[2].

This approach effectively assumes that patients dropped out completely at random, with no interaction between cause of drop-out and treatment outcome. It should be noted that the costs for patients who drop out are included in the base case analysis only up to the point of drop-out[2]. Therefore, the additional costs associated with the assumed survival for drop-outs are not included. As a higher proportion of patients are assumed to survive with micafungin treatment, this would appear to bias the cost elements of the model in favour of micafungin. A subsequent sensitivity analysis has been provided by the company (see section 8.10.1). This is aligned with the published German analysis, which reports some deviations in model outputs from the base case analysis when different approaches to drop-outs are considered, but the overall conclusions remain unchanged[18].

Caspofungin comparison
The full mITT patient population of the caspofungin trial are included in the base case analysis, with just the European sub-group considered in sensitivity analysis. The same approach as with L-AmB comparison has been taken to estimate the overall treatment success rates, which are 59.7% for micafungin and 57.5% for caspofungin. The approach to drop-outs in the base case analysis is the same as for the micafungin – L-AmB comparison, but for the caspofungin comparison, sensitivity analyses have also been presented in the company submisison[2].

8.6.2 Adverse events
It is not specifically stated in the company submission whether or not adverse events have been considered in the analysis of micafungin compared with L-AmB[2]. The published German analysis states that adverse event-related resources were included in the model but little data beyond that are provided[18]. No details of any resource use associated specifically with adverse event data are included in the company submission. For the comparison with caspofungin, resource use associated with treating adverse events were excluded on the assumption that those associated with events with a notably higher prevalence in either treatment arm would be negligible, and other adverse events occurred at a similar frequency in both arms[2].

8.6.3 Utility weights
Utility weights are not assigned to any outcomes in these analyses. The company has highlighted technical difficulties involved in adjusting survival by health-related quality of life.

8.7 Healthcare resource utilisation and cost
Actual patient-level resource use from the clinical trials has been used where possible. All non-drug costs appear to be based on published sources, inflated to 2007 prices where necessary, and drug costs are based on 2007 BNF-listed prices[2].

8.7.1 Drug costs
L-AmB comparison
In the trial of micafungin against L-AmB, antifungal dose increase was permitted after five days (see Table 1A, Appendix 1)[10]. The mean cumulative dose, number of infusions, mean daily dose and number of infusion days from the trial, as reported in

the published German analysis[18] and its UK adaptation[19], have been used in the current model[2]. The British National Formulary (BNF)[6] has reportedly been used to provide the cost/mg for micafungin and L-AmB (AmBisome®), which has been applied to the above mean doses, etc., (although the cost/mg for micafungin reported in the company submission is marginally lower than is estimated from the current BNF list price).

Caspofungin comparison
The trial of micafungin against caspofungin did not permit study drug dose changes (except for patients with hepatic impairment), but patients were permitted to be switched to oral fluconazole after at least 10 days of blinded IV therapy (see Table 1A, Appendix 1)[9]. The BNF-listed drug costs are used in the analysis[2].

8.7.2 Adverse event costs
It is not specified whether or not adverse events are incorporated in the analysis of micafungin compared with L-AmB and no details are provided of any approach to cost adverse event-related resources. For the caspofungin comparison, adverse events and any related costs are not included (see section 8.6.2).

8.7.3 Other resource use and costs
Time spent in intensive care unit (ICU) or non-ICU ward are taken from the trial data. For the caspofungin comparison, ward stay data were not available from the trial so it is assumed for the base case analysis that all patients started on the ICU and stayed there until they were judged to have had a complete or partial clinical response, were switched to oral fluconazole or were determined to have been successfully treated, whichever came first. They were then transferred to the general ward[2]. Other resource use included the costs of sample cultures, IV catheter replacement or removal, scans. Several published sources were used to cost these.

8.8 Discounting
Discounting was not performed as the selected time horizon of analysis was less than one year.

8.9 Results
8.9.1 Base-case analysis: Micafungin versus L-AmB
The model predicts that the average cost per patient is lower with micafungin than with L-AmB (£27,075 versus £29,549) and that the overall effectiveness in terms of treatment success and survival at the end of follow-up is greater with micafungin than with L-AmB (52.9% versus 49.1%). Therefore, micafungin dominates L-AmB[2].

8.9.2 Base case analysis: Micafungin versus Caspofungin
The model predicts that the average cost per patient is marginally lower with micafungin than with caspofungin (£29,095 versus £29,953) and that the overall effectiveness in terms of treatment success and survival at the end of follow-up is greater with micafungin than with caspofungin (59.7% versus 57.5%). Therefore, micafungin dominates caspofungin[2].

8.10 Sensitivity/scenario analyses
8.10.1 One way sensitivity analyses
L-AmB comparison
No one-way sensitivity analyses were presented in the original company submission for the comparison of micafungin with L-AmB[2]. A subsequent analysis has been provided by the company, which indicates that the approach to the handling of patient drop-outs has no impact on the interpretation of the model outputs.

Caspofungin comparison
Three separate approaches to the handling of drop-outs were explored: (i) drop-out patients died at the time of drop-out; (ii) drop-out patients remained alive and consumed the average resources of the completer patients; and (iii) drop-outs were completely excluded from the analysis. In all cases, micafungin still dominated caspofungin.

Two separate approaches to the assumption of hospital ward treatment were explored, which demonstrate that the model is sensitive to the assumptions made around the patient time spent on ICU and general ward:
(i) Patients are split equally between ICU and general ward at start of treatment, all successfully treated patients are assumed to be treated on the general ward, and treatment failures are split equally between ICU and general ward. This resulted in a switch from micafungin being dominant to having an incremental cost per successfully treated patient still alive at the end of follow up of £3,402.
(ii) Length of stay assumed to be equal to the treatment plus follow-up period with all patients assumed to stay on a general ward. This resulted in a switch from micafungin being dominant to having an incremental cost per successfully treated patient still alive at the end of follow up of £24,313[2].

The model provided by the company also includes two further approaches to the assumption of hospital ward treatment, which are not presented in the company submission. It is not clear what scenarios these represent but the model outputs appear to switch from micafungin being dominant in the base case analysis, to having an incremental cost per successfully treated patient still alive at the end of follow up of £14,706 and £40,870.

Additional sub-group analyses have been presented. When the analysis was restricted to just European patients, the model output switched to micafungin having an incremental cost per successfully treated patient still alive at the end of follow up of £2,288. When outputs were explored by APACHE II scores (0-20, >20), age group (18-64 years, 65 years and older) and *Candida* infection (*C. albicans*, non-albicans) micafungin remained dominant. When the analysis was restricted to patients with *C. glabrata*, the model output switched to micafungin having an incremental cost per successfully treated patient still alive at the end of follow up of £7,711[2].

8.10.2 Probabilistic sensitivity analysis (PSA)

L-AmB comparison
The mean cost/patient for micafungin from 1,000 simulations was estimated as £26,807 and effectiveness as 52.9%, whereas the mean cost/patient for L-AmB is reported as £51,535 and effectiveness as 49.0%. It is not clear why there should be such a large increase compared with the base case (deterministic) analysis in the estimated cost/patient with L-AmB. The cost effectiveness acceptability curve indicates that the probability of micafungin being cost effective compared with L-AmB at a willingness to pay of £30,000 per successfully treated patient alive at the end of follow-up (14 to 20 weeks) is 58%[2]. However, as the outcome measure chosen is not the QALY, it is impossible to make any judgement on how this compares with conventional thresholds of cost-effectiveness.

Caspofungin comparison
The PSA predicted a mean cost/patient for micafungin of £29,455 and effectiveness as 59.7%%, and a mean cost/patient for caspofungin of £31,246 and effectiveness of 57.4%. The cost effectiveness acceptability curve indicates that the probability of

micafungin being cost effective compared with caspofungin at a willingness to pay of £30,000 per successfully treated patient alive at the end of follow-up (eight to 14 weeks) is around 58%[2]. However, similarly with the L-AmB comparison, there are difficulties associated with the interpretation of these results.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have identified a published cost-effectiveness analysis of micafungin compared against L-AmB in the treatment of invasive candidiasis and candidaemia in a German hospital setting[18]. A UK adaptation of this has recently been presented at conference[19] and uses the same data and methodology as the L-AmB analysis presented in the company submission[2]. No published evidence on the cost effectiveness of micafungin compared with caspofungin has been identified.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

A simple costing exercise is presented, which uses commercial UK estimates of the annual number of patients treated for candidaemia and applies this proportionally to the Welsh population. It is assumed that there will be no change in the number of patients treated each year, and that all patients are treated for 14 days with IV therapy. Company estimates of uptake are used for the annual costs of micafungin, but the company submission does not estimate the actual net budget impact in each of the five years. No specific consideration is given to the use of micafungin in those cases where the use of other antifungals is not appropriate. The doses of the agents considered in the exercise relate to adult patients only. The company cost estimates over the five years are subject to some uncertainty.

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five year period[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

Data from a commercial database have reportedly been used to estimate that 4,140 patients receive antifungal therapy for Candida bloodstream infections in the UK in one year[20]. Based on the assumption that the Welsh population constitutes 4.8% of the UK population and applying this proportionally to the above figure, it has been estimated that there would be 199 cases in Wales in a given year[2]. It is further assumed that there would be no change in this estimate over the next five years and that incident cases make up the prevalent population due to the discrete nature of infection.

9.3.2 Projected rate of adoption and market share

Based on data from the commercial database[20], it is suggested that the two competitor therapies assumed in this submission, L-AmB and caspofungin, account for the treatment of 78 patients (67 L-AmB; 11 caspofungin). The company submission states that these 78 patients would be the maximum number of patients that would be prescribed micafungin, but acknowledges that this would assume a full product switch to micafungin, which is unlikely[2].

The company submission estimates that uptake in years 1 to 5 would be 5%, 15%, 25%, 40% and 50%[2]. There is no consideration of the extent to which each of L-AmB or caspofungin would be displaced and there is no discussion around the use of

micafungin only when the use of other antifungals is not appropriate[1]. These estimates of uptake would, therefore, appear subject to some uncertainty.

9.3.3 Costs and resource use

The costing exercise considers only the drug acquisition costs of micafungin and the comparators. The company submission notes that the average cost of ICU stay is lower with micafungin (according to the economic model), but that the cost of general ward stay is greater compared with L-AmB and capofungin[2]. This is not further discussed in relation to budget impact.

Data from the commercial database[20] are reported to show that 20% of patients treated with systemic antifungals weigh more than 80kg (although the data that have been provided by the company suggest that 15% of patients weigh more than 80kg. Using 20% would increase the cost of caspofungin against micafungin and L-AmB). BNF list prices[6] are used to cost 14 days of treatment with micafungin (100mg/day irrespective of weight), caspofungin (70mg on day 1 followed by 50mg/day for those 80% of patients weighing ≤80kg, or 70mg/day every day for those 20% of patients weighing >80kg[2]) and L-AmB (3mg/kg/day assuming 70kg patient, using AmBisome®). The L-AmB 14-day costs are estimated on a per mg basis which does not consider potential wastage[2]. Some patients may be eligible to switch from IV to oral antifungals (e.g. fluconazole), at some point during their treatment, which may significantly reduce the overall cost of treatment. This would depend on a number of factors.

9.4 Results

Net resource implications are not estimated. Instead, the company submission simply estimates the costs of treating patients intravenously for 14 days with micafungin, or with L-AmB or with caspofungin based on the number of patients assumed for the rate of uptake in section 9.3.2.

Table 1. Company-estimated costs of micafungin treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated uptake of micafungin	5%	15%	25%	40%	50%
Estimated number of patients (out of 78)	4	12	20	32	40
Cost with micafungin	£19,096	£57,288	£95,480	£152,768	£190,960
Cost with caspofungin	£19,632	£58,896	£98,160	£157,056	£196,320
Cost with L-AmB (AmBisome®)	£22,696	£68,088	£113,480	£181,568	£226,960

The company submission states that the aggregated one-year savings of using micafungin instead of caspofungin and L-AmB would be £61,908, assuming a full product switch for the 11 patients estimated to use caspofungin and 67 patients estimated to use L-AmB. However, the company acknowledges that this is an unlikely scenario[2].

9.5 Sensitivity analysis

No sensitivity analysis was conducted for the budget impact analysis.

9.6 Comparator costs

Micafungin is licensed for use when other antifungals are not appropriate[1]. Table 2 lists examples of other IV agents licensed for the treatment of *Candida* infections and the approximate costs for treating a 70kg adult, based on BNF list costs[6].

Table 2. Example comparator costs

Drugs	Example adult IV dosage	14-day cost[6] for 70kg adult*
Micafungin	100mg/day	£4,774
Caspofungin	70mg day 1, then 50mg/day†	£4,676
Anidulafungin	200mg day 1, then 100mg/day	£4,500
AmBisome®	3mg/kg/day	£5,415
Amphocil®	3-4mg/kg/day	£5,321 - £7,982
Abelcet®	5mg/kg/day	£4,599
Amphotericin B (Fungizone®)	1mg/kg/day‡	£115
Fluconazole	400mg day 1, then 200-400mg/day	£439 to £820 (IV)
Voriconazole	6mg/kg 12 hourly on day 1, then 4mg/kg 12 hourly (IV)	£4,320 (IV)

*Rounded to nearest practical whole dose unit, with wastage.
†Caspofungin dose 70mg daily if patient weighs >80kg[7].
‡ Recommended Fungizone® dose is 250micrograms/kg/day initially, gradually increased to 1mg/kg/day over 2-4 days if tolerated; maximum 1.5mg/kg/day[6]. Assumed 1mg/kg/day here for simplicity.
This table does not imply therapeutic equivalence.
These calculations are based on a VAT rate of 17.5% and do not take into account the recent drop in VAT to 15%.

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- On the basis of the restricted licence of micafungin (for use where other antifungals are not appropriate[1]), consideration may be given to auditing the usage of this product in NHS Wales.
- Micafungin is indicated for the treatment of severe *Candida* infection[1]. It is not suitable for shared care.

10.2 Related advice

Guidelines on the management of patients with invasive fungal infections were issued by the British Society for Medical Mycology in 2003[21]. These do not contain detailed recommendations on the use of agents other than fluconazole and amphotericin-related agents.

The British Committee for Standards in Haematology have recently (2008) issued guidelines on the management of invasive fungal infections in patient with haematological cancer[22]. These suggest that, for all levels of certainty of diagnosis, there is no evidence that any drug has superior efficacy than caspofungin or L-AmB, and that the lowest rates of toxicity are reported for caspofungin followed by L-AmB in trials of empiric treatment of antibacterial-resistant fever of unknown origin[22]. These guidelines were prepared before micafungin was licensed.

Anidulafungin (Ecalta®▼) for the treatment of invasive candidiasis in non-neutropenic adults is scheduled for appraisal by the All Wales Medicines Strategy Group (AWMSG) on 29th April 2009.

10.3 Patient organisation information

A patient organisation submission was not received.

10.4 Other

- The company submission indicates that no new data in the treatment of invasive candidiasis are expected to become available in the next 6-12 months[2].

GLOSSARY

APACHE II score:
Acute Physiology and Chronic Health Evaluation II is a severity of disease classification system that uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. The higher the score (in a range of 0 to 71), the greater the risk of hospital death[23].

Candidaemia:
Infection of the bloodstream by *Candida sp*[24]*.*

Invasive Candidiasis:
Single or multiple organ infection by *Candida sp.* Blood culture may be negative in 40-60% of cases[24].

Incidence:
The number of people falling ill with a specified disease during one year, in a specified population.

Prevalence:
The number of cases of a disease existing in a given population at a specified period of time or at a particular moment in time (point prevalence).

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Appendix 1. Additional Clinical Information

Table 1A. Phase III trials of micafungin in patients with invasive candidiasis

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimens	Outcome (micafungin 100mg od versus comparator)
Micafungin versus caspofungin in adult patients						
9	Randomised, double-blind, phase III, non-inferiority trial Conducted in North America, Europe, Brazil, and India	595 patients randomised (1:1:1) to micafungin 100mg/day or micafungin 150mg/day or caspofungin 578 patients in mITT population; excluded those with *Candida* endocarditis, osteomyelitis, or meningitis, or those with no candidaemia or invasive candidiasis at baseline.	Aged ≥18 years At least 1 blood culture positive for *Candida* organisms, or a diagnosis of noncandidaemic invasive candidiasis, plus ≥1 of: fever (≥38°C), hypothermia (≤36°C), hypotension, local inflammation, radiologic findings suggest invasive candidiasis.	Mean age: 56 years (range 18-95 years) APACHE II score ≤20: 81% Candidaemia: 85% Invasive candidiasis (non-candidaemic): 15% Candida species†: *C. albicans*: 48% Non-*C. albicans*: 55% Neutropenia‡: 9% (11.5% micafungin 100mg od, 5.9% caspofungin). Intravascular catheter in place at baseline: 66%.	Micafungin 100mg od (n=191) or Micafungin 150mg od (n=199) or Caspofungin 70mg od on day 1 followed by 50mg od (n=188) All given IV for 14-28 days (or up to 8 weeks for endophthalmitis or chronic disseminated candidiasis). Investigators encouraged to continue treatment for 14 days after clearance of *Candida* from blood stream and resolution of symptoms. Permitted to switch to oral fluconazole 400mg/day after at least 10 days of blinded IV therapy. Median duration of antifungal treatment was 14 days in the micafungin and caspofungin arms. 20.9% of the micafungin 100mg od arm received oral fluconazole for median of 7.5 days, compared with 21.2% of the caspofungin arm, for a median of 4 days.	**Primary endpoint (mITT analysis)** **Investigator-defined treatment success at end of blinded IV treatment*:** Micafungin 100mg od versus caspofungin od: 76.4% versus 72.3%; difference 4.1% (95% CI -4.4 to 12.3) Non-inferiority criterion met **Other endpoints (mITT analysis):** Micafungin 100mg od versus caspofungin od: **Clinical success** Overall: 87.4% versus 87.2% Candidaemic CR: 78.5% versus 76.4% Candidaemic PR: 9.2% versus 13.0% Non-candidaemic CR: 50.0% versus 57.7% Non-candidaemic PR: 35.7% versus 19.2% **Mycological success** Overall: 88.5% versus 84.0% **Treatment success over time** End of all antifungal therapy: 74.9% versus 70.2% 2 weeks later: 54.5% versus 50.5% 6 weeks later: 46.6% versus 42.6%

Table 1A. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimens	Outcome (micafungin 100mg od versus comparator)
Micafungin versus liposomal amphotericin B in adult patients						
10	Randomised, double-blind, phase III, non-inferiority trial Conducted in North America, Europe, Brazil, India, Thailand, South Africa and Australia	531 patients randomised (1:1) to micafungin 100mg/day or liposomal amphotericin B (L-AmB) 392 patients in PP population, 494 in mITT population.	Aged ≥16 years Clinical signs of systemic *Candida* infection, and had ≥1 positive *Candida* cultures from blood or another sterile site within the previous 4 days. Excluded patients with aminotransferase concentrations 10xULN or bilirubin concentrations 5xULN, or if they had positive cultures only from oropharyngeal, oesophageal, urine, sputum, or bronchoalveolar lavage specimens, or from an indwelling catheter sample	ITT population: Mean age: 55 years (range 16-97 years) APACHE II score ≤20: 74% Neutropenia‡: 12% (13% micafungin 100mg od, 10% L-AmB). PP population: Candidaemia: 85% Invasive candidiasis (non-candidaemic): 15% Candida species†: *C. albicans*: 40% Non-*C. albicans*: 58%	Micafungin 100mg od (n=202 in PP population) or L-AmB 3mg/kg od (n=190 in PP population) Dose fixed for first 5 days; thereafter micafungin and L-AmB could be increased to 200mg od and 5mg/kg od, respectively, for fungal infection persistence. All given IV for 14-28 days (or up to 8 weeks for endocarditis, osteomyelitis, chronic disseminated candidiasis). [if patients weighed ≤40kg, micafungin dosed at 2mg/kg/day, increasing to 4mg/kg/day] In the PP population median duration of antifungal treatment was 15 days in both groups. Dose increase received by 10.9% of the micafungin group and 8.9% of the L-AmB group	**Primary endpoint (PP analysis)** **Investigator-defined treatment success at end of treatment*:** Micafungin 100mg od versus L-AmB od: 89.6% versus 89.5%; difference 0.1% (95% CI -5.9 to 6.2) Non-inferiority criterion met **mITT analysis results:** **Investigator-defined treatment success at end of treatment*:** Micafungin 100mg od versus L-AmB od: 74.1% versus 69.6%; difference 4.5% (95% CI -3.5 to 12.4) **Other endpoints (PP analysis):** Micafungin 100mg od versus L-AmB od: Overall CR: 78.7% versus 77.9% Overall PR: 10.9% versus 11.6% **Treatment success by infection site:** Candidaemia: 90.6% versus 90.8% Invasive candidiasis: 84.4% versus 81.5% **Treatment success by baseline APACHE II score**: ≤20: 92.3% versus 88.5% >20: 79.5% versus 89.2% **Treatment success by baseline neutropenic state:** <500 cells/microL: 75% versus 80% ≥500 cells/microL: 91.6% versus 90.3%

Table 1A. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimens	Outcome (micafungin 100mg od versus comparator)
Micafungin versus liposomal amphotericin B in paediatric patients (not powered for statistical comparisons)						
11	Randomised, double-blind, non-inferiority study (sub-study of phase III trial) Treatment period followed by 12-week follow-up	109 patients enrolled and randomised (1:1) to micafungin or liposomal amphotericin B (L-AmB) 106 patients in the ITT population, 98 patients in mITT population.	Aged <16 years Other criteria as in the phase III study above (ref 10).	mITT population: Age <4 weeks: 14% Age 4 weeks to <2 years: 44% Age 2 to <12 years: 32% Age 12 to <16 years: 10% Neutropenia‡: 19% of mITT population (12.5% micafungin, 26% L-AmB). mITT population: Candidaemia: 93% Invasive candidiasis (non-candidaemic): 7% Candida species†: *C. albicans*: 32% Non-*C. albicans*: 61%	Micafungin 2mg/kg od (n=48) or L-AmB 3mg/kg od (n=50) Dose fixed for first 5 days; thereafter micafungin and L-AmB could be increased to 4mg/kg od and 5mg/kg od, respectively, for fungal infection persistence. All given IV for 14-28 days (or up to 8 weeks for endocarditis, osteomyelitis, chronic disseminated candidiasis). No details on whether permitted to switch to fluconazole therapy. [if patients weighed >40kg, micafungin dosed at 100mg od, increasing to 200mg od] Median duration of antifungal treatment was 15 days in the micafungin arm and 14.5 days in the L-AmB arm.	**Primary endpoint (mITT analysis)** **Investigator-defined treatment success at end of blinded IV treatment*:** Micafungin od versus L-AmB od: Overall: 72.9% versus 76.0% **Treatment success by infection site (mITT analysis):** Candidaemia: 75% versus 76.6% Invasive candidiasis: 50.0% versus 66.7% **Treatment success by baseline neutropenic state (mITT analysis):** <500 cells/microL: 83% versus 77% ≥500 cells/microL: 72% versus 76%

APACHE II score = Acute Physiology and Chronic Health Evaluation II score (see Glossary) ; ITT = intention-to-treat population (all patients who received at least one dose of study drug); IV = intravenous; mITT = modified ITT population (all patients who received at least one dose of study drug and had confirmed *Candida* infection at baseline); od = once daily; PP = per protocol population; ULN = upper limit of normal reference range

*Treatment success defined by the investigators = clinical and mycological success at the end of blinded IV therapy.

Clinical success = complete response (resolution of all attributable signs, symptoms, and abnormal radiographic findings associated with fungal infection [CR]) or partial response (improvement of attributable signs, symptoms, and abnormal radiographic findings since baseline [PR]).

Mycological success = eradication for patients with candidaemia (2 cultures of blood specimens obtained at least 24 h apart had negative results); and presumed eradication for patients with non-candidaemic invasive candidiasis (if the patient had a complete clinical response, including resolution of abnormal radiographic findings present at baseline but no follow up culture or biopsy performed).

†Some patients infected with more than one species. ‡Neutropenia = <500 neutrophils/microL

Non-inferiority criterion = if the two-sided 95% CI for the difference in the proportions (micafungin minus comparator) had a lower bound above –15%.