micafungin 50 and 100mg powder for solution for infusion (Mycamine®) No. (497/08)

Astellas Pharma Ltd

8 August 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

micafungin (Mycamine®) is accepted for restricted use within NHS Scotland. It is restricted to use in the treatment of invasive candidiasis in adults, elderly, and children (including neonates).

Micafungin has been shown to be non-inferior to caspofungin and liposomal amphotericin B in the treatment of patients with invasive candidiasis, the majority of whom had candidaemia and were non-neutropenic. It was effective in the treatment of both *C. albicans* and non-*albicans Candida* species.

micafungin (Mycamine®) is not recommended for use within NHS Scotland for the treatment of oesophageal candidiasis in adult, elderly, and adolescent (≥16 years of age) patients for whom intravenous therapy is appropriate. The manufacturer did not supply any economic analysis and therefore the cost effectiveness could not be assessed.

micafungin (Mycamine®) is not recommended for use within NHS Scotland for prophylaxis of *Candida* infection in adults, elderly, and children (including neonates) 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 manufacturer did not supply any economic analysis and therefore the cost effectiveness could not be assessed.

Overleaf is the detailed advice on this product.

Advice must be treated in strict confidence until published on the SMC website (www.scottishmedicines.org.uk) on **08 September 2008.**

Vice Chairman
Scottish Medicines Consortium

Indication

- Treatment of invasive candidiasis in adults, elderly, and children (including neonates).
- Treatment of oesophageal candidiasis in adult, elderly, and adolescent (≥16 years of age) patients for whom intravenous therapy is appropriate.
- For prophylaxis of *Candida* infection in adults, elderly, and children (including neonates) 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 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.

Dosing information

Invasive candidiasis
100mg daily for bodyweight >40kg or 2mg/kg/daily for bodyweight ≤40kg should be administered 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.

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 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients ≤ 40 kg.

Dosing information for the treatment of oesophageal candidiasis and prophylaxis of *Candida* infection – see manufacturer's Summary of Product Characteristics

Product availability date

July 2008

Summary of evidence on comparative efficacy

Micafungin is a semi-synthetic, echinocandin lipopeptide, antifungal agent. It non competitively inhibits 1,3-beta-D-glucan synthase, an essential component of fungal cell wall synthesis not present in mammalian cells, suggesting a lack of mechanism-based toxicity.

In a phase lll, double-blind, comparative study, 595 patients ≥ 18 years with a diagnosis of candidaemia or non-candidaemic invasive candidiasis were randomised to micafungin 100mg daily, micafungin 150mg daily or caspofungin (70mg loading dose followed by 50mg/day maintenance or 35mg/day maintenance for patients with moderate hepatic insufficiency), and stratified by APACHE score (≤ 20 or > 20). Treatments were administered intravenously for 14 to 28 days (or up to 8 weeks for some indications). The primary efficacy endpoint was treatment success, defined as both clinical and mycological success at the end of blinded intravenous therapy, in the modified intention to treat population (mITT). Clinical success was defined as a complete response (resolution) or partial response (improvement); mycological success was defined as eradication, or as presumed eradication. Non-inferiority of the micafungin regimens to caspofungin was demonstrated if the lower bound of the confidence interval (CI) for the percentage difference in treatment success was greater than -

15%. A Data Review Panel confirmed baseline diagnosis and assessed clinical and mycological outcomes and deaths.

The median duration of treatment was 14 days in each treatment arm. The primary efficacy outcome was achieved by 76% (146/191) of micafungin 100mg patients, 71% (142/199) of micafungin 150mg patients, and 72% (136/188) of caspofungin patients. The treatment difference between micafungin 100mg and caspofungin was 4.1% (95%CI: -4.4% to 12.3%), and between micafungin 150mg and caspofungin -1.0% (95%CI: -9.3% to 7.8%), demonstrating non-inferiority of both micafungin regimens versus caspofungin.

Micafungin had comparable efficacy to caspofungin in both *C. albicans* and non-*albicans Candida* species. There was no difference in the number of emergent and proven relapsed infections.

In another phase lll, double-blind, comparative study, 531 patients with clinical signs of systemic *Candida* infection within the previous 4 days, were randomised to micafungin 100mg daily (2mg/kg/day for patients ≤ 40kg) or liposomal amphotericin B 3mg/kg/day, and stratified by centre, neutropenic status and age. Dose adjustments were permitted after five days, if necessary. Treatment duration was for 14 days to 4 weeks (or up to 8 weeks for some indications). Removal of catheters was recommended.

The primary efficacy endpoint was overall treatment success, defined as both a clinical and mycological response at the end of therapy, in the per protocol (PP) population. Non-inferiority of micafungin to liposomal amphotericin B was concluded if the lower bound of the CI for the percentage difference in treatment success in the PP population (stratified by neutropenic status), was greater than -15%; with confirmatory analysis from the ITT population. Secondary efficacy endpoints included clinical response, mycological response, emergent and recurrent fungal infections during the 12-week follow up and the independent data review board assessment of overall success.

The median duration of treatment was 15 days for both treatments. In the PP population, the primary outcome was achieved by 90% of patients in both the micafungin and liposomal amphotericin B groups (181/202 and 170/190, respectively), with confirmation from the ITT population (72% (189/264) vs. 68% (182/267) for micafungin and liposomal amphotericin, respectively). After stratification for neutropenic status, the difference between the groups was 0.7% (95% CI: -5.3% to 6.7%) in the PP population and 3.9% (95% CI: -3.9% to 11.6%) in the ITT population. Review of the PP results by the independent data review board, reported a 10% lower response rate; the difference stratified by neutropenic status was 1.8% (95%CI: -6.1% to 9.6%).

Mycological persistence at the end of therapy was reported in 9% of patients in both groups. There was no difference in the number of emergent or recurrent infections at the end of therapy or during follow up. Micafungin and liposomal amphotericin B had comparable efficacy in *C. albicans* and non-*albicans Candida* species.

A paediatric sub-study of the above trial was conducted in parallel in patients aged ≤15 years with all treatments being dosed by body weight (micafungin: 2 mg/kg/day; liposomal amphotericin B: 3 mg/kg/day). Candidaemia was the primary infection in the majority of patients. The study was not powered to show a statistical difference between treatment arms. The primary outcome of overall treatment success at the end of treatment was similar in the micafungin and liposomal amphotericin B groups, with 85% (35/41) and 88% (37/42) of the PP population and 69% (36/52) and 74% (40/54) of the ITT population achieving treatment success in the micafungin and liposomal amphotericin groups, respectively. Micafungin showed similar efficacy to liposomal amphotericin B across all age groups,

including neonates; in neutropenic and non-neutropenic patients; against all *Candida* sp. and in candidaemia and invasive candidiasis.

Summary of evidence on comparative safety

In the study with caspofungin, another echinocandin, the adverse event profiles were similar. The safety analysis included 595 patients of whom, 22% and 23% of patients on micafungin 100mg and 150mg and 24% of patients on caspofungin, experienced treatment-related adverse events. The most common (≥ 2% of patients) included an increased serum alkaline phosphatase level, abnormal liver function tests, nausea, constipation, hypokalaemia, and rash. Adverse events that led to withdrawal occurred in 2.5% and 3% of micafungin 100mg and 150mg patients, and 3.6% of caspofungin patients.

In the study with liposomal amphotericin B, there were fewer treatment related adverse events in the micafungin group than the liposomal amphotericin B group and fewer patients withdrew due to adverse events (4.9% vs. 9%). There were statistically fewer cases of rigors, increased serum creatinine, infusion-related reactions, and back pain in the micafungin group.

In the paediatric sub-study, the incidence of treatment-related adverse events was lower in the micafungin than liposomal amphotericin B group (37% vs. 43%) and fewer patients discontinued due to adverse events (3.8% vs. 17%, p=0.052). The most frequently reported treatment-related adverse events were similar to those observed in adult patients.

Mortality rates for caspofungin and micafungin were similar and no deaths were related to study drug. In the study with liposomal amphotericin, there was no difference in mortality rates between treatments but fungal infection was considered to have contributed to the death of 34 (13%) patients on micafungin and 25 (9%) on liposomal amphotericin B. In the paediatric sub-study, mortality was similar between treatment groups.

From a pooled safety analysis of 3028 patients, 10% of whom were children and 13% elderly patients, the European Medicines Agency concluded that: 'Important identified risks are hepatic reactions (elevated liver enzymes), allergic-like reactions, haemolytic reactions and renal adverse events. An important potential risk is the risk for the development of liver tumours. This risk for hepatocarcinogenicity although based on animal studies cannot be excluded for the time being therefore liver function should be monitored carefully during micafungin use.'

Summary of clinical effectiveness issues

Both caspofungin and liposomal amphotericin have been recommended in treatment guidelines for this indication and are appropriate comparators. Micafungin has been shown to be non-inferior to caspofungin and liposomal amphotericin B in the treatment of patients with candidaemia and non candidaemic invasive candidiasis and, in neutropenic and non-neutropenic patients and it was effective in the treatment of both *C. albicans* and non-*albicans Candida* species.

Overall in the two studies, between 75 and 80% of patients had an APACHE score of ≤ 20, approximately 85% had candidaemia and around 90% of patients were non-neutropenic. Therefore the majority of patients in these two studies were not the most seriously ill and although they represent a typical study population, due to the restriction in the marketing authorisation to use only when other antifungals are not appropriate, this population may not represent the patients who will receive micafungin in practice. Patients in the clinical studies

who had non candidiaemic invasive candidiasis, an APACHE score of >20 and were neutropenic still had successful outcomes in the studies but did less well than those who had candidaemia, an APACHE score of ≤ 20 and were non-neutropenic.

The practical advantages of micafungin include its marketing authorisation in children including neonates, it has a low potential to interact with other medications and no requirement for a loading dose or dose adjustments. However it is only available as an intravenous preparation and switching to an oral preparation requires a change of therapy.

Summary of comparative health economic evidence

The manufacturer presented a cost-effectiveness analysis for the treatment of invasive candidiasis, comparing micafungin with caspofungin and with liposomal amphotericin-B using a decision tree. While fluconazole may be the default first line treatment, it is likely that if approved micafungin would displace caspofungin or liposomal amphotericin-B. As a consequence these were appropriate comparators, although it was noted that the marketing authorisation for micafungin restricted use to situations when other antifungals were not appropriate.

The effectiveness parameter chosen was the percentage of patients who were candidiasis treatment successes at end of therapy and who remained alive at end of study, as observed within the modified ITT population of the two clinical trials. For the comparison with liposomal amphotericin-B the patient group was restricted to European and Australian patients.

Resource use data were drawn from the two clinical trials. As the balance between intensive care unit (ICU) and general ward lengths of stay was not collected within the caspofungin trial, this was constructed by inference from among those initially admitted to ICU achieving treatment success or switching to oral fluconazole. The price of micafungin was assumed to be slightly lower than the actual (recently confirmed) price.

For the comparison with caspofungin the manufacturer estimated effectiveness and average patient costs of 60% and £28,916 for micafungin as compared to 58% and £29,953 for caspofungin. For the comparison with liposomal amphotericin-B the manufacturer estimated effectiveness and average patient costs of 53% and £26,838 for micafungin as compared to 49% and £29,549 for liposomal amphotericin-B. As a consequence, the manufacturer asserted dominance for micafungin.

Within the comparison with caspofungin, results were sensitive to the assumptions made as to handling of drop outs and the balance between ICU and general ward length of stays. Overall, there was some uncertainty as to cost effectiveness, with scatter plots from probabilistic analyses showing a dispersion of both net benefits and net costs. However, in many scenarios, micafungin represented a cost-effective treatment option and hence the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology (BCSH) have recently issued guidelines on the management of invasive fungal infection in patients with haematological malignancy. These guidelines recommend liposomal amphotericin B or caspofungin for empirical and proven invasive fungal infections.

The Infectious Diseases Society of America (IDSA) produced guidelines for treatment of candidiasis in 2004. They recommend an amphotericin B preparation, fluconazole or caspofungin for initial medical management. Choice of therapy is guided by weighing the greater activity of amphotericin B–based preparations and the echinocandin antifungal agents for some non–*albicans* species (e.g., *Candida krusei*) against the ready availability of oral and parenteral formulations for the azole antifungal agents. These guidelines are currently being updated and are due to be published in the autumn of 2008.

Additional information: previous SMC advice

Following a full submission, SMC published advice in January 2004: caspofungin (Cancidas®) is accepted for restricted use within NHS Scotland. Casopfungin provides an additional agent for the treatment of invasive candisiasis. Its use should be restricted to patients with fluconazole-resistant *Candida* infection who do not respond to, or cannot tolerate amphotericin B therapy or who are at an increased risk of serious side-effects with amphotericin (eg transplant patients, especially those receiving bone marrow transplants.)

Following a full submission, SMC published advice in August 2005: Voriconazole (Vfend®) is accepted for restricted use within NHS Scotland for the treatment of candidaemia in non-neutropenic patients. Voriconazole provides an additional agent for the treatment of candidaemia in non-neutropenic patients. Its use is restricted to patient with fluconazole-resistant Candida infection who do not respond to or cannot tolerate amphotericin B therapy or who are at an increased risk of serious side-effects with amphotericin.

Following a full submission, SMC published advice in May 2008: anidulafungin (Ecalta®) is not recommended for use within NHS Scotland for the treatment of invasive candidiasis in adult non-neutropenic patients. Anidulafungin has been shown to be at least as effective as an alternative antifungal in a study of patients of whom the majority had candidaemia. However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Additional information: comparators

Other antifungal agents licensed to treat candidiasis are amphotericin B (including AmBisome®, and Amphocil®), fluconazole, caspofungin, anidulafungin and voriconazole.

Cost of relevant comparators

Drug	Dose regimen	Daily costs (£)	14 days treatment cost (£)
Micafungin	**bodyweight >40kg: 100mg daily** **bodyweight ≤ 40kg: 2mg/kg/day**	**341** **196**	**4774** **2745 - 4774**
AmBisome®	Adult: 3mg/kg/day Child: 3mg/kg/day	387 193	5415 2707
Amphocil®	Adult:3 to 4mg/kg/day Child: 3 to 4mg/kg/day	380-484 190	5321 to 6779 2661
Caspofungin	Adult only: 70mg loading dose then 50mg daily	417 328	4676
Anidulafungin	Adult only: 200mg on day 1 then 100mg daily	600 300	4500
Voriconazole	Adult: 6mg/kg 12hourly on day 1 then 4mg/kg 12 hourly child 2 to12 years:7mg/kg every 12 hours	390 231 154-231	3317 2160 to 3240
Fluconazole	Adult: 400mg on day 1 then 200 to 400mg daily child: 6 to12mg/kg/day neonate 2 to 4 weeks: 6 to12mg/kg/48hours neonate up to 2 weeks: 6 to12mg/kg/72 hours	59 29-59 29-59 7-15 7-15	439 to 820 410 to 820 102 to 154 29 to 59
Amphotericin B	Adult and child: 1mg/kg/day	8	58 to115

Doses are based on a patient weighing 25 kg or 60kg and a neonate up to 7kg. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2nd June 2008.

Additional information: budget impact

The manufacturer estimated a net drug cost of £17k for invasive candidiasis based upon 30 patients switching from caspofungin, this being balanced by a net drug saving of £48k based upon 114 patients switching from liposomal amphotericin B, yielding an overall net drug cost saving of £31k. These estimates were based on a treatment duration longer than that which may be used in clinical practice and as such any realisable savings may be lower than the figures presented.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 18 July 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

The European Medicines Agency (EMEA) European Public Assessment Report. Micafingin (Mycamine®) EMEA/H/C/000734 www.emea.europa.eu

Pappas PG et al. Micafungin versus Caspofungin for Treatment of Candidemia and Other Forms of Invasive Candidiasis. *Clinical Infectious Diseases*. 2007; 45 (1 October):883-93

Kuse E et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *The Lancet*. 2007; 369:1519-27