Scottish Medicines Consortium

caspofungin 50mg and 70mg powder for concentrate for solution for infusion (Cancidas®) No. (147/04)

Merck Sharp & Dohme

New indication: *empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult patients.*

10 December 2004

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

ADVICE: Following a full submission

Caspofungin (Cancidas®) is accepted for restricted use within NHS Scotland for the empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult patients. It should be restricted to patients under the care of specialists experienced in the management of fungal disease.

A comparative study found that caspofungin was as effective as a lipid formulation of amphotericin in terms of overall response. In addition it was better tolerated with fewer drug-related adverse events including less nephrotoxicity and infusion-related events. It is less expensive than another formulation of liposomal amphotericin, which has a licence for empirical use.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Caspofungin 50 and 70mg vials (Cancidas®)

Licensed indication under review:

Empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult patients.

Dosing information under review:

A single 70mg loading dose should be administered on day 1, followed by 50mg daily thereafter. In patients weighing > 80kg, 70mg daily is recommended after the initial 70mg loading dose. Caspofungin should be administered by slow intravenous infusion over approx. 1 hour. The duration of empirical therapy should be based on the patient's clinical response. Therapy should be continued until up to 72 hours after resolution of neutropenia (ANC ≥ 500). Patients found to have a fungal infection should be treated for a minimum of 14 days and for ≥ 7 days after both neutropenia and clinical symptoms are resolved.

UK launch date

Not applicable as this is a new indication for an existing medication.

Comparator Medications

Conventional amphotericin (not licensed for this indication) and lipid formulations of amphotericin, of which only AmBisome® is specifically licensed. Abelcet® and Amphocil® are other lipid forms of amphotericin but are not specifically licensed for empirical use.

Cost per treatment period and relevant comparators

Based on doses for 70kg adult	Basic NHS Cost/day
Caspofungin 50mg daily*	**£328**
AmBisome® 3mg/kg/day (210mg)	£692 (assumes 5 x 50mg vials)
Amphotericin 1mg/kg/day (70mg)	£7.40 (assumes 2 x 50mg vials)
Abelcet® 5mg/kg/day (350mg)	£296 (assumes 3 x 100mg + 1 x 50mg vials)
Amphocil® 3mg/kg/day (210mg)	£484 (assumes 2 x 100mg + 1 x 50mg vials)

* after a loading dose of 70mg on day 1 (£416.78)
Contract prices may be available in hospitals.

Summary of evidence on comparative efficacy

The efficacy data to support the use of caspofungin for empirical therapy in febrile, neutropenic patients comes from the results of one randomised, double-blind non-inferiority study. Eligible patients were ≥ 16 years and had received chemotherapy for cancer or had undergone haemopoietic stem cell transplantation. A total of 1095 patients with persistent fever (>38ºC despite parenteral antibacterial therapy for at least 96 hours) and neutropenia (defined as an absolute neutrophil count (ANC) <500cells/mm^3 for at least 96 hours) were enrolled. Patients were stratified according to risk (high risk- those who had undergone allogeneic stem-cell transplant or with relapsed acute leukaemia; or low risk- all others) and use of systemic antifungal prophylaxis before being randomised to receive caspofungin 50mg once daily (following a 70mg loading dose) or liposomal amphotericin (AmBisome®) 3mg/kg/day. In patients with no evidence of baseline or breakthrough fungal infection, therapy was continued until up to 72 hours after resolution of neutropenia (to a maximum of 28 days). In patients with a documented fungal infection, therapy was continued as determined necessary by the investigator but the protocol recommended at least 14 days and for at least seven days after resolution of neutropenia and symptoms (to a maximum of 90 days).

The primary endpoint was a favourable overall response to a five-component composite:

1. successful treatment of any baseline fungal infection
2. absence of any breakthrough fungal infection during therapy or within seven days of stopping
3. survival for seven days after stopping therapy
4. no premature discontinuation because of drug related toxicity or lack of efficacy
5. resolution of fever (<38ºC) for at least 48 hours during neutropenia.

Response was considered favourable if all five components of the composite were met.

An overall favourable response, when adjusted for strata, was reported in 34% (190/556) caspofungin patients and 34% (181/539) AmBisome® patients (difference 0.2% [95.2% CI: -5.6%, 6.0%]). The overall response rates were higher in high risk than low risk patients in both groups and were numerically higher in the caspofungin group. In the high risk patients, 43% (63/146) caspofungin and 38% (46/122) AmBisome® patients responded (difference 5.4% [95.2% CI: -6.3%, 17%] compared to 31% (127/410) and 32% (135/417) respectively in low risk patients. Prior antifungal prophylaxis had no significant effect on overall response.

Three of the components of the primary endpoint favoured caspofungin therapy over AmBisome®; namely successful treatment of baseline fungal infections (52% versus 26%), survival for seven days post-therapy (93% versus 89%) and discontinuation due to toxicity or lack of efficacy (10% versus 14%).

There were a total of 24 baseline infections due to *Aspergillus* species and response rates to therapy were 42% (5/12) in caspofungin patients and 8.3% (1/12) in AmBisome® patients. *Candida* species were also responsible for 24 baseline infections of which 67% (8/12) responded to caspofungin and 42% (5/12) to AmBisome®. There were a number of breakthrough infections due to uncommon yeasts or unidentified moulds (n=4 with caspofungin and n=1 with amphotericin B). The distinction between baseline and breakthrough infections was arbitrarily defined as onset up to the second day of study therapy versus onset after the third day.

Summary of evidence on comparative safety

During the key study, caspofungin was associated with significantly fewer drug related adverse events than AmBisome® (54% versus 69%, p<0.001) and fewer caspofungin patients discontinued therapy due to drug toxicity (5% versus 8% respectively, p=0.04).

There was less nephrotoxicity (defined as a doubling of the serum creatinine level or in patients with elevated baseline serum creatinine, an increase of ≥1mg/dl) following treatment with caspofungin than AmBisome® (2.6% versus 12%; difference –8.9%; 95% CI: -12%, -5.9%, p<0.001). Infusion-related events, most notably fever, chills, headache, nausea and vomiting were also significantly less in the caspofungin group (35% versus 52%; difference –16%; 95% CI: -22%, -0.7%, p<0.001).

Summary of clinical effectiveness issues

The key study used a composite endpoint of five components which has been described by the European Medicines Agency (EMEA) as a means of providing an idea of the overall utility of the drug in febrile neutropenic patients. While it is recognised that it is difficult to assess the true efficacy of empirical therapy, the EMEA issued advice indicating that this should be based solely on the successful treatment of any fungal infection documented pre-treatment. In addition, current EMEA guidelines state that studies should be designed to demonstrate superiority over the comparator but the study was conducted prior to this advice being issued.

In terms of the individual components of the composite, a favourable outcome may not necessarily reflect efficacy of the antifungal drug. These patients have many confounding factors. For example, resolution of fever may reflect response to concomitant successful antibacterial therapy, resolution of a drug-induced fever, recovery of the neutrophil count, or successful treatment of underlying disease. Similarly favourable survival is not necessarily a direct consequence of the efficacy of empirical antifungal therapy.

Caspofungin has demonstrated efficacy against *Aspergillus* and *Candida* species but there are a number of other less common yeasts and moulds against which efficacy has not been demonstrated.

Summary of comparative health economic evidence

The economic model is a cost minimisation analysis. This is supported by evidence from a large randomised controlled trial with direct comparison to liposomal amphotericin B, which is widely used in the NHS in Scotland for this indication.

The model suggests that caspofungin may be cost saving and will have better clinical outcome with significantly reduced risk of nephrotoxicity and a trend towards a reduction in mortality.

Budget Impact

The estimated annual savings are £775,000 in the first year increasing to over £2 million by year 5

Existing or proposed guidelines and protocols

Caspofungin was launched in July 2002 for the treatment of invasive aspergillosis in adult patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. In March 2003, the SMC advised that caspofungin was not recommended for use for this indication.

In February 2003, the licence was extended to include the treatment of invasive candidiasis in non-neutropenic adult patients. In January 2004, the SMC advised that caspofungin is accepted for restricted use in 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 (e.g. transplant patients, especially those receiving bone marrow transplants).

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 1 December, 2004.

Drug prices are those available at the time of SMC assessment.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

Walsh TJ, Teppler H, Donowitz GR et al. Caspofungin versus liposomal amphoericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004; 351: 1391-402

Klastersky J.Antifungal therapy in patients with fever and neutropenia – more rational and less empirical? Editorial. N Engl J Med 2004; 351: 1445-7.