Re-Submission

anidulafungin 100mg powder and solvent for concentrate for solution for infusion (Ecalta®) No. (465/08)
Pfizer Ltd

10 October 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 re-submission

anidulafungin (Ecalta®) is accepted for restricted 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, the majority of whom had candidaemia. Its use is restricted to patients who are unable to tolerate fluconazole or have invasive candidiasis that is resistant to fluconazole.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of invasive candidiasis in adult non-neutropenic patients.

Anidulafungin has been studied primarily in patients with candidaemia and only in a limited number of patients with deep tissue *Candida* infections or with abscess-forming disease.

Dosing information

A single 200mg loading dose on day one, followed by 100mg daily thereafter administered by intravenous infusion. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

Treatment with anidulafungin should be initiated by a physician experienced in the management of invasive fungal infections.

Product availability date

December 2007

Summary of evidence on comparative efficacy

Anidulafungin is a semi-synthetic echinocandin antifungal agent which acts by inhibiting fungal cell wall biosynthesis. It has in vitro activity against *Candida* species including *C. albicans, C. glabrata, C. parapsilosis and C. tropicalis.*

The key evidence comes from the results of a double-blind, randomised, non-inferiority study in patients with a diagnosis of candidaemia (defined as at least one positive blood culture) or other forms of invasive candidiasis (defined as positive culture obtained from a sterile site) within 96 hours before enrolment. Eligible patients also had at least one of the following: fever, hypothermia, hypotension, local signs and symptoms or radiologic findings of invasive candidiasis. Patients were randomised in a 1:1 ratio to receive intravenous anidulafungin (200mg on day one, followed by 100mg daily, n=131) or intravenous fluconazole (800mg on day one, followed by 400mg daily, n=125) for 14 to 42 days (and for at least 14 days after a negative blood culture and improvement in signs and symptoms). Randomisation was stratified according to Acute Physiology and Chronic Health Evaluation (APACHE II) scores (≤20 or >20) and absolute neutrophil count (≤500 or >500 cells/mm^3). After at least ten days of intravenous therapy, all patients could switch to oral fluconazole (400mg daily) at the investigators discretion provided they could tolerate oral medication, had been afebrile for ≥24 hours, last blood culture was negative for *Candida* species, and if there was clinical improvement.

The primary endpoint was the successful global response (clinical and microbiological) at the end of intravenous therapy in the microbiological intention-to-treat (micro-ITT) population (all patients who received at least one dose of study medication and had a positive *Candida* culture at baseline). Clinical success was defined as cure or improvement of signs and symptoms of *Candida* infection and no need for additional antifungal therapy or further oral fluconazole. Microbiological success was defined as eradication (documented by negative cultures for all *Candida* species present at baseline or presumed by successful clinical response where culture data were not available). Anidulafungin would be considered non-inferior to fluconazole if the lower limit of the 95% confidence interval (CI) calculated around the difference in global response rates was greater than –20%. If non-inferiority was

demonstrated, then a further test for superiority was pre-specified, where the lower limit of the 95% CI of the difference was > 0.

The mean duration of intravenous therapy was 13.5 days for anidulafungin and 12.1 days for fluconazole; 26% (33/127) and 28% (33/118) of patients respectively switched to oral fluconazole. The primary endpoint of global success in the micro-ITT population at the end of intravenous therapy was 76% (96/127) in the anidulafungin group and 60% (71/118) in the fluconazole group, corresponding to a difference of 15% (95% CI: 3.8% to 27%). A separate analysis in an evaluable population (defined as a subset of the micro-ITT population with no protocol violations) found global success rates of 87% (90/103) and 75% (68/91) respectively at the end of IV therapy, corresponding to a difference of 13% (95% CI: 1.7% to 24%).

The European Medicines Agency (EMEA) reported results of a separate post hoc analysis using a revised definition of clinical success as those with cure only (i.e. patients with improvement only were classified as failures). The results were consistent with those of the primary analysis in terms of non-inferiority, but not superiority, (68% (86/127) versus 58% (68/118) for anidulafungin and fluconazole respectively: difference 10% (95% CI: -2.0% to 22%).

Global success rates in the anidulafungin and fluconazole groups of the micro-ITT population at other time-points were 74% (94/127) and 57% (67/118) at the end of all therapy; 65% (82/127) and 49% (58/118) after 2 weeks follow-up and 56% (71/127) and 44% (52/118) after 6 weeks follow-up respectively.

Summary of evidence on comparative safety

In the key study described above, the number of treatment-related adverse events was similar in both groups (24% in the anidulafungin group and 26% in the fluconazole group). The most frequently reported treatment-related adverse events in the anidulafungin group were hypokalaemia (3.1% (4/131)), diarrhoea (3.1% (4/131)) and elevated alanine transaminase (ALT) (2.3% (3/131)), while in the fluconazole group they were elevated hepatic enzymes (7.2% (9/125)), elevated alkaline phosphatase (4.0% (5/125)) and elevated ALT (3.2% (4/125)). Treatment-related hepatic enzyme elevations were significantly more common in the fluconazole group (7.2% vs. 1.5%).

Treatment-related serious adverse events were reported in two patients in each group; in the anidulafungin group, one patient had atrial fibrillation and another seizures; while in the fluconazole group, one had deep vein thrombosis and another elevated hepatic enzymes.

Summary of clinical effectiveness issues

Applying the pre-specified criteria to the results of the pivotal study demonstrated that anidulafungin was firstly non-inferior and then superior to fluconazole in terms of the primary outcome at the end of intravenous therapy. The primary endpoint of global success comprised clinical and microbiological response with a successful clinical response defined as either cure or improvement. The EMEA analysis, using a stricter definition of clinical success (as cure only), demonstrated consistent results for non-inferiority but did not go on to support the claim for superiority since the lower limit of the 95% CI was not >0.

The primary efficacy outcome was measured at the end of intravenous therapy which fails to include the impact of recurrence or re-infection. It may have been preferable to assess efficacy after a follow-up period of least 2 weeks after treatment. Secondary analysis included assessment at later time points (end of all therapy, and after 2 and 6 weeks follow-

up) which provided results generally consistent with the primary analysis although the global success rates were reduced.

Most of the patients in the pivotal study had APACHE scores ≤20 (>80%), indicating less severe disease. Also the majority of patients (>90%) had the most basic form of candidiasis (i.e. candidaemia). Therefore, there is limited evidence of the efficacy of anidulafungin in patients with deep tissue *Candida* infections or with abscess-forming disease.

There are no comparative data with other echinocandins e.g. caspofungin.

The licensed indication for anidulafungin is currently narrower than the indications approved for alternative antifungals. However anidulafungin offers advantages over other antifungals in terms of dosing, with no dosage adjustments necessary in patients with renal or hepatic impairment. In addition there are no known drug interactions with anidulafungin.

An economic analysis is presented for the use of anidulafungin as a second-line agent, but there are no specific clinical data for use in this setting. Patients could be enrolled if they had received previous antifungal therapy but this was not a requirement, and the duration of treatment could not exceed 72 hours prior to randomisation.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis examining the use of anidulafungin as a second-line treatment option for patients who are unable to tolerate fluconazole or have invasive candidiasis that is resistant to fluconazole, or are severely ill. Comparators in the analysis were caspofungin, voriconazole, amphotericin B and liposomal amphotericin B, all of which were appropriate and a comparison was also presented with fluconazole. The second-line positioning of the drug was appropriate given its premium price over fluconazole, to which clinical trial evidence shows it is non-inferior, but it should be noted that the clinical evidence for anidulafungin is not specifically in the niche sought.

The manufacturer used an informal indirect comparison to support an assumption that anidulafungin was as effective as the comparator treatments in terms of treatment cure or success and hence why a cost-minimisation was deemed appropriate. However, on the basis of an indirect comparison, rates of nephrotoxic side effects differed between treatments such that anidulafungin and fluconazole had zero rates of nephrotoxicity but all other comparators had rates varying between 8.4% and 24.8%. Each nephrotoxic event was assumed to cost around £7200. Treatment duration for voriconazole, caspofungin and amphotericin B (conventional and liposomal) was assumed to be the same as for anidulafungin at 13.5 days.

The results of the analysis indicated that anidulafungin would be preferred on cost-minimisation grounds to both caspofungin and liposomal amphotericin B (savings of £772 and £2375 respectively). Anidulafungin was however more expensive than fluconazole, voriconazole and conventional amphotericin B and hence would not be preferred to these treatments. The results were relatively stable in sensitivity analysis even when the probability of nephrotoxicity and the cost of such events were varied. The treatment duration with caspofungin would have to be 10 days or less for anidulafungin not to be the preferred treatment to caspofungin or 7 days or less in the case of the liposomal amphotericin B comparison.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Infectious Diseases Society of America (IDSA) issued updated guidelines for treatment of invasive candidiasis in 2008. They recommend fluconazole or an echinocandin (caspofungin, anidulafungin, micafungin) for initial medical management.

Additional information: previous SMC advice

Following a full submission, the Scottish Medicines Consortium (SMC) issued advice in January 2004: caspofungin is accepted for restricted use within NHS Scotland. Caspofungin provides an additional agent for the treatment of invasive candidiasis. 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 (e.g. transplant patients, especially those receiving bone marrow transplants).

Following a full submission, the Scottish Medicines Consortium (SMC) issued 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 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.

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in June 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.

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in September 2008: 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.

Additional information: comparators

Alternative antifungals used in invasive candidiasis are listed in the cost table below.

Cost of relevant comparators

Drug	Dose regimen	Cost per 14-day course (£)
Anidulafungin	**200mg IV on day 1 then 100mg daily**	**4500**
Amphocil®	3-4mg/kg/day IV	5321 to 7982
AmBisome®	3mg/kg/day IV	5415
Micafungin	bodyweight >40kg: 100mg daily bodyweight ≤ 40kg: 2mg/kg/day	4774 2745 to 4774
Caspofungin	70mg IV on day 1 then 50mg daily	4676
Abelcet®	5mg/kg/day IV	4599
Voriconazole	6mg/kg 12hourly IV on day 1 then 4mg/kg 12 hourly	4320
Fluconazole	400mg IV on day 1 then 200-400mg daily	439 to 820
Amphotericin B	1mg/kg/day IV	115

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7th August 2008 or from Monthly Index of Medical Specialities August 2008. IV = intravenously. Weight-based doses assume a body weight of 70kg.

Additional information: budget impact

The manufacturer estimated that the gross drug budget impact of using anidulafungin was £65k in year one rising to £170k in year five. After taking account of the cost of existing treatments, the net cost was estimated at £1k in year 1 rising to £3k in year 5. 195 patients were assumed to be eligible for treatment each year and the market share was estimated at 8% in year 1 rising to 20% by year 5 i.e. 16 patients in year one rising to 39 patients by year 5.

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 29 August 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 reference was supplied with the submission. The reference shaded is additional to those supplied with the submission.

Reboli AC, Rotstein C, Pappas GP et al., Anidulafungin versus Fluconazole for Invasive Candidiasis. *NEMJ* 2007;**356**:2472-2482.

European Medicines Agency (EMEA). European Public Assessment Report (EPAR) for anidulafungin. www.emea.eu.int