Scottish Medicines Consortium

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

Pfizer Ltd

09 May 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

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.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of invasive candidiasis in adult non-neutropenic patients.

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.

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 >500mm^{-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, 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 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 timepoints (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.

The non-inferiority margin selected in the pivotal study is relatively wide at 20% and the EMEA comment that a narrower value might have been preferable. However the chosen value was reported to be influenced by previously reported studies in echinocandins.

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 seriously ill patients or patients with infections of sites other than the bloodstream.

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

The licensed indication for anidulafungin is currently much 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.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis of anidulafungin relative to fluconazole for the treatment of candidiasis. This used a markov model with a daily cycle. The results of this were presented for three time horizons of 8 weeks, 6 months and 12 months. The results were presented for all patients, and for a subset of ITU patients.

The 8 week success rates from the pivotal trial were used to estimate the daily likelihood of patients having their candidiasis eradicated. Those patients not succeeding with their 1st line treatment could progress to 2nd line amphotericin B, the probability of this being derived from the literature. Second-line amphotericin B might cure their candidiasis, but might also cause them to develop nephrotoxicity. For those cured of their candidiasis there remained an elevated mortality risk during their remaining hospital stay due to their underlying condition. The likelihood of dying in hospital and the likelihood of discharge were taken from the literature. Quality of life values were not collected during the trial, and were instead estimated using an algorithm based on APACHE II scores. Other costs were from recognised sources, though large nephrotoxicity costs of £22k per event were derived from US sources.

From this the manufacturer estimated that the use of anidulafungin conferred small average patient gains across the patient group as a whole of around 0.001 QALYs at the 8 week point, rising to 0.011 QALYs at the 12 month point. Due to savings from reduced nephrotoxicity events anidulafungin was also estimated to confer small cash savings of £123 at the 8 week point, this rising to savings of £350 at the 12 month point.

Within a subgroup requiring ITU care, patient benefits were estimated to be slightly larger: 0.003 QALYs at the 8 week point, rising to 0.021 QALYs at the 12 month point. The anticipated cost savings from anidulafungin also rose due to reduced ITU length of stay: of £1,147 at the 8 week point, this rising to £1,732 at the 12 month point. The corollary to this was that among general ward patients anidulafungin was not cost-saving but resulted in cost increases, despite significant savings from reduced nephotoxicities still being anticipated.

The manufacturer also presented a cost-minimisation analysis of anidulafungin relative to caspofungin, voriconazole, conventional amphotericin B and liposomal amphotericin B. These were assumed to be clinically equivalent in terms of success rates, but caspofungin, voriconazole, conventional amphotericin B and liposomal amphotericin B were associated with increased risks of nephrotoxicity, the risks of these being estimated from the literature. The results indicated that anidulafungin was found to be cost- saving.

The model was clearly presented with a reasonable structure. However, there were a number of weaknesses within the analysis. These included:

- apparently assuming treatment successes were cures, when a number may have only been improvements and in whom candidiasis might recur, which given joint reductions in

cure rates across both anidulafungin and fluconazole could significantly worsen cost effectiveness of anidulafungin.
- there was no consideration of 2nd line use of anidulafungin despite its price premium over fluconazole;
- efficacy data to support the cost-minimisation analysis in terms of clinical success rates being equivalent between treatments and evidence of comparability of patient populations were not presented;
- a cost of £22,775 per nephrotoxicity event among those receiving 2nd line amphotericin B this being derived from US resource use and unit costs associated with acute renal failure, the reference cited indicating an increased cost from nephrotoxicity alone of only $8947.

Given these issues, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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) produced guidelines for treatment of candidiasis in 2004. They recommend an amphotericin B preparation, fluconazole or caspofungin for initial medical management. These guidelines are currently being updated. Anidulafungin was not available at the time of publication of this guidance.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 12 January 2004 that caspofungin was 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).

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 8 August 2005 that 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.

Additional information: comparators

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

Cost of relevant comparators

Drug	Dose regimen	Cost per day (£)	Cost per 14 day course (£)
Anidulafungin	**200mg on day 1 then 100mg daily**	**600 300**	**4500**
AmBisome®	3mg/kg/day	387	5415
Amphocil®	3-4mg/kg/day	380-484	5321-6779
Caspofungin	70mg on day 1 then 50mg daily	417 328	4676
Abelcet®	5mg/kg/day	246	3449
Voriconazole	6mg/kg 12hourly on day 1 then 4mg/kg 12 hourly	309 231	3317
Fluconazole	400mg on day 1 then 200-400mg daily	59 29-59	439-820
Amphotericin B	1mg/kg/day	8	115

Doses are based on an adult patient weighing 60kg. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29.2.08 except anidulafungin and caspofungin costs which are from MIMS February 2008.

Additional information: budget impact

Based upon an estimate of 53 patients being eligible and a market share of 15% in year 1 rising to 75% by year 5, the manufacturer estimated a gross drug cost of £23k for year 1 rising to £129k by year 5.

Given cost offsets from the reduced use of other antifungal drugs, the cost of which was anticipated to fall by approximately £146k in year 1 to £45k in year 5. The manufacturer estimated a net drug cost of £800 for year 1 rising to £4,600 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 17 April 08.

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 grey is additional to those supplied with the submission.

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

European Medicines Agency (EMEA). European public assessment report (EPAR) for anidulafungin. www.emea.eu.int