All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Anidulafungin (Ecalta®▼) for the treatment of invasive candidiasis in adult non-neutropenic patients

Pfizer UK Ltd

Advice No: 0809 – April 2009

Recommendation of AWMSG

Anidulafungin (Ecalta®▼) is recommended as an option for use within NHS Wales within its licensed indication for the treatment of invasive candidiasis in adult non-neutropenic patients.

AWMSG is of the opinion that anidulafungin (Ecalta®▼) is not suitable for shared care within NHS Wales.

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, 29th April 2009

The recommendation of AWMSG is:

Anidulafungin (Ecalta®▼) is recommended as an option for use within NHS Wales within its licensed indication for the treatment of invasive candidiasis in adult non-neutropenic patients.

AWMSG is of the opinion that anidulafungin (Ecalta®▼) is not suitable for shared care within NHS Wales.

ABBREVIATIONS

ALT	Alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CI	Confidence interval
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
HPA	Health Protection Agency
ICU	Intensive care unit
ITT	Intention-to-treat
ITU	Intensive treatment unit
IV	Intravenous
mITT	Modified intention-to-treat
MTC	Mixed treatment comparison
OR	Odds ratio
SPC	Summary of Product Characteristics

2.0 PRODUCT DETAILS

2.1 Licensed indication

Treatment of invasive candidiasis in adult non-neutropenic patients[1].

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[1].

2.2 Dosing

Specimens for fungal culture should be obtained prior to therapy. Therapy may be initiated before culture results are known and can be adjusted accordingly once they are available[1].

Anidulafungin should be reconstituted as directed in the Summary of Product Characteristics (SPC). A single 200mg loading dose should be administered by intravenous (IV) infusion on day one, followed by 100mg daily by IV infusion thereafter. It is recommended that the rate of infusion does not exceed 1.1 mg/minute. Anidulafungin should not be administered as a bolus injection[1].

Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. There are insufficient data to support the 100mg dose for longer than 35 days of treatment[1].

2.3 Market authorisation date

Marketing authorisation was granted by the European Medicines Agency (EMEA) on 20th September 2007[2].

2.4 UK Launch date

7th December 2007

3.0 DECISION CONTEXT

Invasive fungal infections are increasing in frequency in all western countries. This is due to a variety of factors, including the increasing use of invasive technologies and indwelling intravascular catheters, and the use of broad-spectrum antibiotics[2,3]. *Candida* species have emerged as one of the leading causes of nosocomial blood stream infections (candidaemia). *C. albicans* is the predominant clinical pathogen but the proportion of infections caused by non-*albicans* species has increased exponentially over the last decade[2]. The shift in the epidemiology of *Candida* infections, and increasing emergence of resistant strains, has important clinical and therapeutic implications[2]. If the infection is unresponsive to treatment, it can spread from the blood stream to the liver, kidney, spleen, bones, muscles, joints and eyes, and can lead to organ failure[3].

Several antifungal agents are licensed for the treatment of invasive candidiasis, but not all are indicated and/or recommended for first-line use for all *Candida* species[2,4]. Fluconazole (IV and/or oral routes) is indicated for *C. albicans* infection in clinically stable patients who have not received an azole antifungal recently. This agent has been used widely, which has led to the emergence of resistant strains (e.g. *C. krusei*

and *C. glabrata*[2]). Amphotericin B can be given by IV infusion against all species, but there are issues of renal toxicity with the conventional formulation (Fungizone®), and alternative lipid-based preparations (Abelcet®, AmBisome®, Amphocil®), which may reduce this risk, are significantly more expensive than the conventional amphotericin formulation. Caspofungin (IV route) or 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. In refractory cases, IV flucytosine can be used in combination with amphotericin[3,4].

Anidulafungin is an echinocandin antifungal agent, which inhibits fungal cell wall biosynthesis. This action differs from other classes of antifungals and, to date, there has been no documented report of resistance to anidulafungin in clinical study isolates or non-clinical study isolates of *Candida* species. Development of cross-resistance with agents from other classes is not expected[2]. In contrast to fluconazole, anidulafungin does not require dose adjustment in patients with renal insufficiency or those on dialysis[1]. It also appears to have a low potential for drug interactions[2]. Two other echinocandins are currently licensed: caspofungin and micafungin. Caspofungin and micafungin are both licensed for use in the treatment of invasive candidiasis in adults and children, irrespective of neutropenic status. However, due to the potential risk of developing liver tumours, the licensed indication for micafungin stipulates that it should only be used if other antifungals are not appropriate[5].

Following consultation between WMP and the company, the scope of the appraisal was revised in line with current practice. Anidulafungin is therefore considered within the submission as an alternative treatment option for patients who have failed fluconazole, and in whom caspofungin might be an alternative,

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The pivotal phase III non-inferiority study VER002-9 compared IV anidulafungin against IV fluconazole in adult patients with invasive candidiasis (primarily candidaemia due to *C. albicans*). The primary endpoint was global success at the end of IV therapy, defined as combined clinical and microbiological success in the modified intention-to-treat (mITT) population (n=245). This was achieved in 75.6% of patients in the anidulafungin group and 60.2% of the fluconazole group (difference 15.42%, 95% confidence interval [CI] 3.85 to 26.99), meeting the pre-specified criteria for non-inferiority and superiority to fluconazole (p=0.01). Results at two and six week follow up were consistent with this finding, although the global success rates were lower in both groups over time and were no longer statistically significantly different between groups at six weeks. Other secondary and sub group analyses were also consistent with the primary findings. Almost all patients experienced an adverse event but there was no significant difference in the occurrence of treatment related adverse events (24.4% versus 26.4%), including serious adverse events.

4.2 Review of the evidence on cost-effectiveness

A cost minimisation analysis has been presented of second-line treatment with anidulafungin compared with caspofungin and micafungin in patients who have failed on fluconazole. The basis of this analysis is an indirect comparison of the efficacy of anidulafungin with caspofungin and micafungin. This is considered by the company to

demonstrate that there is no difference between the three antifungals except in relation to the drug acquisition costs and management of adverse effects.

The company submission reports total treatment costs of £10,712 for anidulafungin, £11,483 for caspofungin, and £10,965 for micafungin treatment, i.e. treatment costs with anidulafungin are reported to be lower than with either caspofungin or micafungin. However, there are a number of limitations to the analysis. The clinical evidence that is available for anidulafungin, and the comparators in this analysis, does not relate specifically to its use as a second-line agent in patients who have failed fluconazole. Furthermore, there are no direct comparative studies of anidulafungin against other echinocandins, and so estimates of the relative effectiveness of anidulafungin is limited to indirect comparisons only, which are acknowledged by the company as being weaker than estimates obtained from direct comparisons. The model appears to be relatively stable to the parameter values explored in sensitivity analyses.

5.0 LIMITATIONS OF DECISION CONTEXT

- Patients with *C. krusei* were excluded from the pivotal phase III trial due to known fluconazole resistance and there were low numbers of non-*albicans* isolates other than *C. glabrata*. The relative efficacy of anidulafungin against these *Candida* species is therefore not definitive[2].
- Patients with *Candida* endocarditis, osteomyelitis or meningitis were specifically excluded from the pivotal trial. Less than 10% of included patients had invasive candidiasis that extended beyond the blood stream, and less than 20% had Acute Physiology and Chronic Health Evaluation (APACHE II) scores >20. There is limited data on the use of anidulafungin in such patients.
- There are no direct comparative data against antifungal agents/regimens other than fluconazole.
- The economic evidence relates only to comparisons of anidulafungin against other echinocandins and does not relate to other agents that may be feasible alternatives in the clinical circumstances that are modelled.

6.0 CLINICAL EVIDENCE

6.1 Clinical efficacy

The company submission provides details of the pivotal phase III trial (VER002-9, n=261) used to support the licensed indication for anidulafungin[7,8]. A phase II, dose-ranging study (VER002-6, n=123), and an open-label phase III study in patients who would have been excluded from the pivotal phase III trial (VER002-9B, n=33) are also included[9,10]. Table 1A of Appendix 1 provides an overview of these. As the latter two studies provide only limited, non-comparative data, these are not considered below. Additional data was included within the company submission and provided to members but remains commercial in confidence.

6.1.1 Pivotal phase III trial of anidulafungin and fluconazole (study VER002-9)[8]

This was a double-blind, randomised, multicentre, non-inferiority trial of anidulafungin against fluconazole in 261 adult patients with invasive candidiasis. Patients were stratified at baseline by APACHE II score (≤20 or >20) with higher scores indicating more severe disease), and by absolute neutrophil count (≤500 or >500 cells/mm^3). Only around 20% of patients had APACHE II scores >20 and only around 2% were

classed as neutropenic (≤500 cells/mm^3). Approximately 90% of patients had candidaemia only, defined by at least one positive blood culture, with the remainder having other forms of invasive candidiasis. *C. albicans* was the most common pathogen (around 62% of cases) [2]. Patients with *C. krusei* isolates were excluded, due to the known resistance of this species to fluconazole; however, exclusion of patients with *C. glabrata*, which is also often resistant to fluconazole, was at the discretion of the investigating physician guided by local hospital protocols[2]. Around 16% of those who received anidulafungin and 25% of those who received fluconazole had *C. glabrata* isolates at baseline[8].

Of 261 randomised patients, 245 made up the mITT population used for the primary endpoint analysis (anidulafungin n=127, fluconazole n=118). This population included patients who had received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site preferably within 96 hours before entry into the study[2,8]. Patients received IV anidulafungin at a loading dose of 200mg on day one followed by 100mg once daily, or IV fluconazole at a loading dose of 800mg on day one followed by 400mg once daily (with dose adjustments made for those with renal insufficiency). Antifungal treatment was administered for at least 14 days after the last negative blood culture and improvement of clinical signs and symptoms; the maximum treatment duration permitted was 42 days. Therapy was encouraged to be completed with IV study medication, if possible. Patients in either group, however, could be switched to oral fluconazole (400 mg/day) after at least 10 days of IV treatment if they were afebrile for at least 24 hours, were able to tolerate oral medications, their last blood culture was negative for *Candida* species, and the investigator felt it was appropriate to do so[2].

The primary endpoint was successful global response, defined as combined clinical and microbiological success in the mITT population at the end of IV therapy. Clinical success included cure (resolution of signs and symptoms with no further antifungal therapy required) and improvement (significant but incomplete resolution of signs and symptoms, with no further antifungal treatment required). Microbiological success included confirmed eradication, or presumed eradication where culture data were not available for a patient with a successful clinical response. Non-inferiority was to be declared if the lower limit of the 95% CI for the difference in successful global response between anidulafungin and fluconazole was not less than -20%. It was pre-specified that if the lower limit of the 95% CI was greater than zero, then anidulafungin would be considered superior to fluconazole. Secondary efficacy endpoints included global response and clinical response at the end of both IV and oral therapy, at two week follow up and at six week follow up and microbiological response at patient and pathogen level[2].

Results

Overall, 74% of the mITT population randomised to anidulafungin and 62% of patients randomised to fluconazole completed a full course of treatment (IV and oral where relevant)[2]. The mean duration of IV treatment was 13.5 and 12.1 days in the anidulafungin and fluconazole groups, respectively[8]. Thirty three patients (approximately 27%) in each group were switched to oral fluconazole, with a mean duration of oral treatment of 9.2 and 7.97 days, respectively[7].

Global success at the end of IV therapy was 75.6% for anidulafungin versus 60.2% for fluconazole (difference 15.4%, 95% CI 3.9 to 27.0; see Table 1A, Appendix1). Anidulafungin therefore met the pre-specified criteria for non-inferiority to fluconazole

for the primary endpoint. As the 95% CI for the difference in global success rates was above zero, the response rate was statistically significantly greater for anidulafungin (p=0.01)[8]. All secondary endpoints indicated that anidulafungin was at least non-inferior to fluconazole[2] (see Table 1B, Appendix 1[11]).

Among those with a baseline APACHE II score of ≤20, a successful response at the end of IV therapy was seen in 82/101 (81.2%) of the anidulafungin group and 60/98 (61.2%) of the fluconazole group. Among the few patients with a baseline APACHE II score >20, the proportion of those with a successful response was similar in the two groups (anidulafungin: 14/26 [53.8%] versus fluconazole: 11/20 [55.0%])[2,8]. No statistical analyses were conducted to determine the significance of these results.

A *post hoc* analysis was undertaken to determine the influence of the definition of clinical success as used in the primary endpoint. When the definition of clinical success was restricted only to those patients who were cured (i.e. excluding those who experienced improvement only), anidulafungin was no longer statistically superior to fluconazole for the endpoint of global response, but the difference met the criterion for non-inferiority (86/127 [67.7%] versus 68/118 [57.6%], difference 10.09% [95% CI -1.98 to 22.16])[2]. Other *post hoc* analyses were undertaken in those patients who were receiving immunosuppressive therapy[2], those who received antifungal therapy within an intensive care unit [ICU] setting at study entry, and in those with hepatic, renal and respiratory impairment[7,12]. There was a trend for global response rates for anidulafungin to be numerically greater than fluconazole in these groups, though patient numbers were low.

Points to note

- Exclusion criteria included patients who had received prophylactic azole antifungal therapy for more than one week in the 30 days before enrolment and those who had received more than 48 hours of antifungal treatment for their current *Candida* infection (later changed to 72 hours). Patients with meningitis were excluded because the blood-brain permeability of anidulafungin has not been fully defined[2].
- Although the protocol allowed for treatment duration up to 42 days, the maximum exposure to anidulafungin was 35 days (three patients were treated for 29-35 days)[2].
- The margin of 20% used to define non-inferiority was considered in the European Public Assessment Report (EPAR) to be wide and assessment of the primary end point after at least two weeks would have been preferable to at the end of IV therapy. Anidulafungin was statistically superior for the primary endpoint and non-inferiority was consistently demonstrated for all secondary endpoints at two and six week follow up, although the global response rates decreased over time[2].
- Although patients in this study were ill, and many had comorbidities, around 90% had candidaemia only, most were non-neutropenic and most had APACHE II scores ≤20.
- *C. albicans* was the baseline pathogen in 62% of patients and, of the non-*albicans* species, *C. glabrata* was the most frequently isolated (around 20% of patients). Fluconazole has a narrower spectrum of activity than echinocandins and *C. glabrata* is often resistant to this drug. There were very few non-*albicans* isolates other than *C. glabrata*[2].

6.2 Safety

Almost all patients experienced an adverse event in the pivotal phase III trial and the number of patients in the ITT population experiencing treatment related adverse events was similar in the two treatment groups (59 events in 32 patients [24.4%] in the anidulafungin group and 64 events in 33 patients [26.4%] in the fluconazole group)[8]. These included hypokalaemia (3.1% anidulafungin versus 2.4% fluconazole), diarrhoea (3.1% versus 1.6%), and infusion related events as noted in the SPC[1], such as flushing (1.5% versus 1.6%) and pruritus (1.5% versus zero)[11,16]. Elevations in hepatic enzymes were observed significantly more frequently in the fluconazole group (1.5% versus 7.2%),(p=0.03)[8]. However, the actual number of events was low, which warrants caution in the interpretation. Given the short term use of anidulafungin, the risk of irreversible liver injury is considered low and in line with that for fluconazole in the patient populations studied[2]. The SPC recommends that patients with increased hepatic enzymes during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy[1].

Across the three studies in invasive candidiasis (VER002-9, VER002-6, VER002-9B), a pronounced higher incidence of gastrointestinal adverse events was observed in anidulafungin recipients compared with the fluconazole recipients (nausea: 21.6% versus 11.2%; vomiting: 16.2% versus 9.2%)[2]. The EPAR also refers to higher rates of respiratory distress (3.3% versus 0.7%) and dyspnoea (5.8% versus 1.4%) with anidulafungin than with fluconazole[2].

Around 50% of patients in each group of the pivotal phase III study experienced serious adverse events, the most common of which were cardiac arrest (3.8% versus 8.8%), multi organ failure (3.1% versus 4.0%), respiratory failure (2.3% versus 4.8%), sepsis (2.3% versus 6.4%), septic shock (0.8% versus 6.4%) and acute renal failure (zero versus 4.8%) within the anidulafungin and fluconazole groups, respectively[16]. The serious adverse events were only considered treatment related in two patients from each group (anidulafungin: atrial fibrillation and seizures; fluconazole: deep vein thrombosis and increased hepatic enzymes)[8].

Adverse events leading to discontinuation of the study drug in the pivotal phase III trial occurred in 27 patients (21.6%) receiving fluconazole and 15 (11.5%) receiving anidulafungin (p=0.02)[8,16]. Of these, four patients in the fluconazole group and one in the anidulafungin group discontinued due to treatment related adverse events[16]. In the mITT population, 29/127 patients (22.8%) in the anidulafungin group and 37/118 (31.4%) in the fluconazole group died (p=0.13, NS). Median time to death was 21 days and 14 days, respectively[8]. Two deaths were considered to be due to *Candida* infection in the anidulafungin group and five in the fluconazole group[1].

Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes[1] and has demonstrated a low potential for drug-drug interactions[2]. No dosage adjustment is recommended when anidulafungin is co-administered with ciclosporin, voriconazole or tacrolimus, and no dosage adjustment for anidulafungin is recommended when co-administered with amphotericin B or rifampicin[1]. The SPC notes the high alcohol content of reconstituted anidulafungin and lists precautions for its use in relevant groups[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Fluconazole and amphotericin B (and lipid formulations of amphotericin) would appear to be the main comparators for anidulafungin. Caspofungin and voriconazole are also licensed for use in invasive candidiasis, but may not be suitable for first-line use (see section 3.0). Micafungin is also licensed for use in invasive candidiasis, but due to the potential risk of developing liver tumours, the licensed indication for micafungin stipulates that it should only be used if other antifungals are not appropriate[5].

7.2 Comparative effectiveness

- The pivotal phase III trial did not include patients from the UK, although there is no reason to suggest that the results of the trial are not applicable to the Welsh population.
- Patients with *C. krusei* were excluded from the pivotal trial and there were low numbers of non-*albicans* isolates other than *C. glabrata*. The efficacy of anidulafungin against these species is therefore not definitive but, to date, there have been no documented reports of resistance to anidulafungin in clinical study isolates or non clinical study isolates of *Candida* species[2].
- Patients with *Candida* endocarditis, osteomyelitis or meningitis were specifically excluded from the pivotal trial. Less than 10% of included patients had invasive candidiasis that extended beyond the blood stream, less than 20% had APACHE II scores >20, and very few were neutropenic. There is limited data on the use of anidulafungin in such patients and no direct comparative data against antifungal agents/regimens that may be used in these patients other than fluconazole.
- The global success rate in the pivotal phase III study was statistically superior with anidulafungin than with fluconazole at the end of IV therapy, at two week follow up, but not at six week follow up. The success rates decreased in both treatment groups over time.
- Discontinuation of treatment due to adverse events was less frequent with anidulafungin than with fluconazole, but not when treatment related adverse events were considered. Although not statistically significant, more patients completed a full course of treatment and the mean duration of treatment was longer with anidulafungin than with fluconazole.
- In contrast to fluconazole[17], amphotericin B related formulations[18-21], voriconazole[22] and micafungin, anidulafungin is not licensed for use in patients less than 18 years of age due to limited data in this population. Its use in pregnancy is not recommended[1].
- In contrast to fluconazole and some other antifungal agents, anidulafungin does not require dose adjustment for renal insufficiency and appears to have a low potential for interaction with other drugs[1]. This is an important consideration in the treatment of many patients in the ICU setting. The reconstituted product, however, has a significant alcohol content (24 vol% ethanol) which should be taken into account in high risk groups and may alter the effects of some medicines[1].
- The safety data on anidulafungin is rather limited compared with the long established agents fluconazole and amphotericin B. Overall, the available data suggest that the adverse event profile of anidulafungin is similar to that of fluconazole, with the exception of higher rates of respiratory distress and dyspnoea in the former[2].

- There are no ongoing studies for the current indication for which results will be available in the next six to 12 months.

8.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by anidulafungin over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of anidulafungin is acceptable.

8.2 Description and critique of the company's submission

The company submission[7] describes a cost minimisation analysis that compares anidulafungin against caspofungin and micafungin as second-line agents in patients who have previously failed on fluconazole treatment. It is assumed that the differences between anidulafungin and these other agents relate only to the drug acquisition costs and the management of adverse effects, which are only considered to be nephrotoxic. It is assumed that patients who experience nephrotoxicity whilst taking caspofungin or micafungin are switched to anidulafungin. Total duration of antifungal treatment, irrespective of the agent used, is assumed to be 13.5 days, as was observed in the pivotal trial of anidulafungin (study VER002-9).

There are a number of limitations to the cost minimisation analysis. The clinical evidence that is available for anidulafungin, and the comparators in this analysis, does not relate specifically to its use as a second-line agent in patients who have failed fluconazole. Furthermore, there are no direct comparative studies of anidulafungin against other echinocandins, and so estimates of the relative effectiveness of anidulafungin is limited to indirect comparisons only, which are acknowledged by the company as being weaker than estimates obtained from direct comparisons.
The model has been provided by the company and appears to be relatively stable to the parameter values explored in sensitivity analyses.

Additional data was included within the company submission and provided to members but remains commercial in confidence.

8.3 Population

The company submission states that the population considered in the cost analysis reflects patients who have failed previously on fluconazole treatment and would be eligible to receive an echinocandin[7]. It should be noted that the efficacy data for anidulafungin are derived from the main clinical trial of anidulafungin (study VER002-9 – see section 6), in which patients were randomised to either IV anidulafungin or fluconazole[8]. The efficacy data for anidulafungin, therefore, do not relate specifically to its second-line use following failure of fluconazole (see section 8.6.1).

8.4 Perspective and time horizon

The analysis is conducted from the perspective of NHS Wales. A time horizon of only two weeks following initiation of antifungal treatment has been assumed on the basis that invasive candidiasis is an acute condition[7]. Invasive candidiasis can be life threatening and, although there are difficulties in modelling beyond the two week treatment period in the trial, it is unlikely that the two week time horizon will capture all relevant costs and outcomes. However, it is acknowledged that an implicit assumption

of the cost minimisation analysis is that there are no differences in survival between treatments.

8.5 Comparator

The analysis considers anidulafungin compared against caspofungin and micafungin. All are echinocandins[1,23,5] and may be used second-line. However, it should be noted that the licensed indication for micafungin states that, due to a potential risk for the development of liver tumours, it should only be used if other antifungals are not appropriate[5].

8.6 Clinical inputs

8.6.1 Efficacy data

There are no direct comparative data for anidulafungin and the comparators caspofungin or micafungin. A cost minimisation analysis has been conducted, in which it is assumed that the only differences between anidulafungin and the comparators is in the acquisition costs and the management of adverse events.

The company submission acknowledges that these comparisons are weak[7], but still considers the results to be sufficiently compelling to form the basis of the economic evidence that is presented.

8.6.2 Adverse events

The only adverse effect considered in this analysis is nephrotoxicity[7]. The company submission states that there were no reported cases of serious, treatment-related nephrotoxicity with anidulafungin treatment in study VER002-9, and so no costs associated with this adverse effect are accrued for anidulafungin[7]. In the absence of published rates of nephrotoxicity with micafungin treatment, an incidence rate of zero percent is assumed[7]. For caspofungin, a literature search was reportedly undertaken to identify published estimates of nephrotoxicity. The trial of caspofungin compared against conventional amphotericin B, used in the indirect MTC, has been used to provide an incidence estimate of 8.4%[13]. Nephrotoxicity is costed as acute renal failure in this cost minimisation analysis (see section 8.7.2). The definition of a nephrotoxic effect in the trial providing an incidence rate of 8.4% with caspofungin was a serum creatinine level that was twice the baseline value or higher, or an increase of at least 1mg per decilitre (88.4micromol per litre) in patients with a base line serum creatinine level above the upper limit of the normal range[13]. Sensitivity analyses have been conducted around the base case assumptions of the incidence of nephrotoxicity[7].

8.6.3 Utility weights

As a cost minimisation analysis is presented, utility weights are not incorporated.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

British National Formulary (BNF)[4] list prices of drugs are used to cost the mean number of days of treatment with each antifungal agent.

In study VER002-9, the mean duration of IV anidulafungin treatment was 13.5 days, and in the 26% of patients who switched to oral fluconazole (as permitted in the study protocol), the mean duration of oral therapy was 9.2 days[8].

It is assumed that the mean duration of treatment with IV caspofungin or micafungin would also be 13.5 days[7]. It should be noted that the mean duration of caspofungin

treatment in the trial that compared it with conventional amphotericin B was 12.1 days[13], and in the trial against micafungin the median duration of treatment was 14 days for both antifungals[14]. For micafungin, in the trial against liposomal amphotericin B, the median duration of treatment was 15 days[15]. Sensitivity analysis has been conducted around the duration of treatment with caspofungin and micafungin[7].

It is assumed that patients who experience nephrotoxic effects with caspofungin would switch to anidulafungin treatment. In the base case analysis, it is assumed that this would occur after three days of caspofungin treatment, but the total duration of IV antifungal therapy would remain 13.5 days (i.e. three days of caspofungin followed by 10.5 days of anidulafungin)[7]. The number of days before a switch of therapy has been tested in sensitivity analyses[7].

8.7.2 Adverse event costs

The costs of nephrotoxicity are based on the costs of acute renal failure associated with amphotericin B, as estimated in a tertiary care centre in the USA in 2000[24]. The cost estimated in 2000 has been converted from US dollars to pounds sterling using the exchange rate at that time, and has then been inflated to the 2006/7 value[7]. The extent to which this cost reflects the cost of nephrotoxic effects of caspofungin in Wales is unclear, and has been tested in sensitivity analysis[7].

8.7.3 Other resource use and costs

Hospital costs associated with the management of *Candida* infections are based on the length of hospital stay for antifungal treatment as used in an economic evaluation of caspofungin compared with liposomal amphotericin B in the UK[25]. On the basis of this evaluation, it is assumed that patients who do not experience serious side effects spend two extra days in hospital following IV antifungal therapy and that the average stay on ICU would be 0.3 days[25], with the remainder of the time spent on a general ward. Therefore, in the current cost minimisation analysis, it is estimated that total hospital stay would be 15.5 days, 0.3 days of which would be on ICU and 15.2 days of which would be on a general ward[7].

The company submission does not refer to the costs of hospital stay in those patients who experience nephrotoxicity. The model provided by the company indicates that this is available as an input in line with the assumptions used in the published economic analysis of caspofungin compared with liposomal amphotericin B[25].

The costs of stay on these different ward types is estimated using Scottish National statistics, and is composed of weighted averages of general surgery and general medicine ward costs for the general medicine ward costs in this analysis, and high dependency and ICU cost for the ICU costs in this analysis[7]. It is unclear why Scottish costs have been used when estimates for England and Wales are available, although it is unlikely this would significantly alter the overall conclusions from the current analysis.

8.8 Discounting

Costs and outcomes have not been discounted as the time horizon of the analysis is less than 12 months[7].

8.9 Results

8.9.1 Base case analysis

The company submission reports total treatment costs of £10,712 for anidulafungin, £11,483 for caspofungin and £10,965 for micafungin treatment, i.e. treatment costs with anidulafungin are reported to be lower than with caspofungin or micafungin.

8.10 Sensitivity analysis

8.10.1 One- and two-way sensitivity analyses

A range of one- and two-way sensitivity analyses have been conducted, which indicates that the model is relatively stable to the parameter values that have been tested.

The company submission reports that varying the probability of nephrotoxicity with anidulafungin and micafungin in the range 0-8%, and with caspofungin in the range +/- 50% of the baseline probability, did not change the conclusion that anidulafungin was the least expensive of the three antifungal treatments.

Varying the duration of treatment with caspofungin and micafungin indicates that anidulafungin remains the least expensive treatment while every treatment with caspofungin exceeds 10 days and treatment with micafungin exceeds 12 days. The time taken to switch from caspofungin treatment to anidulafungin due to nephrotoxicity had no impact on the results of the analysis.

8.10.2 Probabilistic sensitivity analysis (PSA)

Not applicable.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of anidulafungin.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

Health Protection Agency (HPA) data for 2007 provides estimates of the number of reported cases of candidaemia in Wales. It is assumed that this will remain constant, that 85% receive antifungal treatment, which is fluconazole, and that half of these cases would be resistant to, or fail fluconazole for other reasons. Company estimates of the number of these cases that would be treated with anidulafungin are then applied. No consideration is given to potential displacement of other agents. The estimates of budget impact are essentially based on several assumptions and would appear subject to some uncertainty.

9.2 Perspective and time horizon

The analysis considers the budget impact from the perspective of NHS Wales over a five year period[7].

9.3 Data sources

9.3.1 Incident and prevalent cases

As episodes of *Candida* infection are acute, it is assumed that the annual incidence is the same as the prevalence. HPA data indicates that there were 91 cases of candidaemia in Wales in 2007[26]. These data relate only to *Candida* in the blood stream and do not provide estimates of the total number of cases of invasive candidiasis. In the company submission it is assumed that the incidence will remain constant over the next five years, which would seem contrary to current trends; there was a 4% increase in reported cases between 2006 and 2007[26].

It is assumed that 85% of cases of *Candida* infection are treated with antifungals[7], on the basis of a prospective, one-year survey of *Candida* blood stream infections in Scotland[27]. It is then simply assumed in the company submission that all would receive fluconazole and that 50% of these cases would require second-line treatment due to fluconazole failure (approximately 38 cases)[1]. However, it should be noted that the Scottish survey found that around 77% of those who received antifungal therapy received fluconazole[27].

9.3.2 Projected rate of adoption and market share

The company simply estimates that 20 cases would be treated with anidulafungin.

9.3.3 Costs and resource use

Based on the costs and treatment durations assumed in the base case cost minimisation analysis (see section 8), the total cost of treatment with anidulafungin is estimated to be £4,352 per case. This includes the small additional costs of oral fluconazole.

The total costs for caspofungin (£5,213) and micafungin (£4,514) are also reported.

9.4 Results

The company submission reports that the total cost of treating 20 cases of candidaemia with anidulafungin would be approximately £87,000 per year. It is assumed that this will be constant in each of the five years. Given the range of assumptions employed this would appear subject to a degree of uncertainty that is not further explored.

9.5 Sensitivity analysis

No sensitivity analyses have been conducted for the budget impact estimates.

9.6 Table of comparative unit costs

The company submission refers only to other echinocandins as comparators for anidulafungin. It is feasible that voriconazole would be a comparator under the clinical circumstances being modelled. Table 2 provides comparative costs for a 14 day course of IV treatment.

Table 2. Comparative costs for a 14 day IV course

Drug	Dose regimen*[4]	14 day cost*[4]
Anidulafungin	200mg day 1, then 100mg/day	£4,500
Caspofungin	70mg day 1, then 50mg/day	£4,676
Micafungin	100mg/day	£4,774
Voriconazole	6mg/kg every 12 hours on day 1, then 4mg/kg every 12 hours	£4,320†

Doses shown above are for general comparison and do not imply therapeutic equivalence.
*Assuming 70kg adult; †Assuming possible vial wastage and dose rounding
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

Anidulafungin is indicated for the treatment of severe nosocomial *Candida* infection. 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[28]. These do not contained detailed recommendations on the use of agents other than fluconazole and amphotericin related agents.
- Ministerial ratification of the following AWMSG advice remains outstanding pending clarification: 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).

10.3 Other

Although only a small number of patients are predicted to be eligible for treatment for invasive candidiasis in the company submission, anidulafungin does not have ultra-orphan drug status[7].

10.4 Patient organisation information

A patient organisation submission was not received.

GLOSSARY

Acute Physiology and Chronic Health Evaluation (APACHE II):
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[29].

Candidaemia:
Infection of the bloodstream by *Candida sp*[30]*.*

Clinical success:
Resolution of signs and symptoms of invasive candidiasis with no need for additional systemic antifungal therapy[7,8].

Global success:
Combined clinical and microbiological success[7,8].

Incidence:
The rate at which new cases occur in a population during a specified period[31].

Invasive Candidiasis:
Single or multiple organ infection by *Candida sp.* Blood culture may be negative in 40-60% of cases[30].

Microbiological success:
Eradication of candida species present at baseline, as determined on follow-up culture, or the presumed eradication, if culture data were not available for a patient with a successful clinical response[7,8].

Prevalence:
The proportion of a population that are cases at a point in time[31].

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APPENDIX 1. ADDITIONAL CLINICAL INFORMATION

Table 1A. Prospective studies of anidulafungin in invasive candidiasis

Ref	Study type	No. of patients	Study population	Treatment regimen	Outcomes
8	Pivotal Phase III randomised, double-blind, active-controlled, multicentre trial	Total randomized: 261 mITT: 245	Patients ≥16 years with candidaemia or other forms of invasive candidiasis Mean age: 58 years Male: 51% APACHE II scores ≤20: Approx. 80% Candidaemia only: Approx. 90% *C. Krusei* excluded	Arm 1: Anidulafungin (n=127) IV 200mg on day 1 and then 100mg daily Arm 2: Fluconazole (n=118) IV 800mg on Day 1 and then 400mg daily IV drugs were administered for at least 10 days and then patients could switch to oral fluconazole. Antifungal therapy given for at least 14 days after a negative blood culture and improvement in signs and symptoms.	**Primary outcomes:** Global success at end of IV therapy*, n (%): Anidulafungin 96 (75.6%) versus fluconazole 71 (60.2%), difference 15.4% (95% CI 3.9 to 27.0) **Secondary outcomes:** See table 1B, Appendix 1
9	Phase II, randomised, dose-ranging study	Total randomised: 123 ITT population: 120	Patients ≥18 years with candidaemia or other forms of invasive candidiasis Median age: 52-59 years Male: 43% APACHE II scores ≤20: Approx. 75% Candidaemia only: Approx. 94% *C. Krusei* included (4% of isolates at baseline)	Randomised to Anidulafungin IV 50, 75 or 100mg daily Treatment continued for 2 weeks after resolution of the infection, and blood and tissue cultures were negative, or presumed to be negative if not obtainable.	**Primary outcomes:** Successful global response rate (clinical and microbiological success) in the evaluable population at 2 weeks after end of therapy. At 2 weeks after end of therapy, the success rates were 72, 85, and 83%
10	Phase III, open-label, non-comparative study	Planned enrolment: 66 Actually enrolled: 33 ITT: 33 mITT: 31	Patients ≥18 years with candidaemia or other forms of invasive candidiasis Mean age: 54.5 years Male: 65% APACHE II scores ≤20: Approx. 81% Candidaemia only: Approx. 90% *C. Krusei* included (3% of isolates at baseline)	Anidulafungin IV 200mg on day 1 and then 100mg daily administered for at least 10 days, at which point patients could switch to oral fluconazole. Antifungal therapy was given for at least 14 days after a negative blood culture and improvement in signs and symptoms.	**Primary outcomes:** Global response at the end of IV therapy in the mITT population: 67%

APACHE II= Acute Physiology and Chronic Health Evaluation; CI= confidence interval; ITT= intention-to-treat; mITT= modified intention-to-treat; *Combined clinical and microbiological success in the mITT population at the end of IV therapy.

Table 1B. Selected secondary endpoint data from study VER002-9[2,7,8,11]

Response	Anidulafungin: n (%)	Fluconazole: n (%)	Difference: % (95% CI)
Global success rates[2,7,8]			
End of oral therapy	31/33 (93.9)	28/33 (84.8)	9.09 (-5.60 to 23.79)*
End of all therapy	94/127 (74.0)	67/118 (56.8)	17.24 (5.49 to 28.99), p<0.02
2 week follow up	82/127 (64.6)	58/118 (49.2)	15.41 (3.14 to 27.68), p<0.02
6 week follow up	71/127 (55.9)	52/118 (44.1)	11.84 (-0.60 to 24.28), NS
Microbiological success rates by *Candida* species[7.8]			
C. albicans	77/81 (95.1)	57/70 (81.4)	p=0.01
C. glabrata	15/20 (75.0)	18/30 (60.0)	NS
C. tripicalis	13/15 (86.7)	7/11 (63.6)	NS
C. parapsilosis	9/13 (69.2)	14/16 (87.5)	NS
*= p value not provided ; NS= not significant.			

Additional data was included within the company submission and provided to members but remains commercial in confidence.