

Horizon Scanning Technology Briefing

*National
Horizon
Scanning
Centre*

**Anidulafungin for
invasive candidiasis
and candidaemia**

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**UNIVERSITY OF
BIRMINGHAM**

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

Anidulafungin for invasive candidiasis and candidaemia

Target group

- Invasive candidiasis and candidaemia in adults (all species including those resistant to azoles and amphotericin B).

Background

Invasive candidiasis is an opportunistic, predominantly nosocomial fungal infection that occurs when *Candida* species, normally found in the digestive tract, enter the bloodstream. *Candida* can also be introduced into the body through contaminated medical equipment or devices. Once in the bloodstream, infection spreads to the liver, kidney, spleen, bones, muscles, joints and eyes, and can lead to organ failure if the infection is undiagnosed or unresponsive to treatment. Immunocompromised patients, including those with AIDS and cancer are particularly vulnerable. Candidaemia is the most basic form of invasive candidiasis, and is where *Candida* has entered the bloodstream but has not yet infected the organs. Initial symptoms of infection can be non-specific.

Invasive life-threatening fungal infections are increasing in frequency in all western countries. This is due to a variety of factors, including increasing use of invasive technologies and the use of broad-spectrum antibiotics. It is believed that there has also been a rise in the non-*albicans* species of *Candida* with reduced susceptibility to fluconazole^{1,2}.

Technology description

Anidulafungin (Eraxis – US only) is a novel echinocandin in development for the treatment of invasive *Candida* infections (all species including those resistant to azoles e.g. fluconazole and voriconazole, and amphotericin B). Anidulafungin selectively inhibits an enzyme that synthesises glucan, a major structural component of the fungal cell wall. It is administered as a once daily intravenous infusion with a loading dose of 200mg on day 1 followed by 100mg per day until clinical response. Treatment is usually continued for 14 days after the last positive fungal culture. No dose adjustment is required for patients with renal/hepatic impairment, unlike the majority of current treatments. Anidulafungin can also be given at any time during haemodialysis.

Caspofungin (Merck Sharp Dohme) is the only other echinocandin currently licensed in the UK for invasive candidiasis but, due to toxicity issues, its use is only indicated after failure of fluconazole and amphotericin. Micafungin (Astellas), another echinocandin, is in phase III clinical development for candidiasis.

Anidulafungin is also in phase III development for the treatment of invasive *Aspergillus fumigatus*.

Innovation and/or advantages

Anidulafungin is active against strains of *Candida* resistant to currently available drugs. If improved efficacy compared to fluconazole is translated into reduced length of hospital stay, this together with its improved side-effect profile and compatibility with other drugs (rifampicin, cyclosporin and tacrolimus, or other antifungal agents) may make it a first treatment of choice.

Developer

Pfizer Ltd.

Place of use

- | | | |
|--|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis | <input type="checkbox"/> Community or residential care e.g. district nurses, physio | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses |
| <input checked="" type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter | <input type="checkbox"/> Other: | |

Availability, launch or marketing dates, and licensing plans:

Pre-registration in the EU. The FDA approved it for use in February 2006.

NHS or Government priority area:

- | | | |
|---|---|--|
| <input type="checkbox"/> Cancer | <input type="checkbox"/> Cardiovascular disease | <input type="checkbox"/> Children |
| <input type="checkbox"/> Diabetes | <input type="checkbox"/> Chronic conditions | <input type="checkbox"/> Mental health |
| <input type="checkbox"/> Older people | <input type="checkbox"/> Public health | <input type="checkbox"/> Renal disease |
| <input type="checkbox"/> Women's health | <input checked="" type="checkbox"/> None identified | <input type="checkbox"/> Other: |

Relevant guidance

- Infectious Disease Society of America. Guidelines for Treatment of Candidiasis, 2004³.
- The British Society for Medical Mycology. National standards of care for patients with invasive fungal infections, 2003⁴.

Clinical need and burden of disease

Between 1997 and 2002, candidaemias were the eighth most common cause of hospital-acquired bloodstream infection in the UK⁵. Incidence of invasive candidiasis rose from 6.8 to 13.7 per million population in England and Wales between 1990-1999 (equivalent to approximately 780 cases)⁶. In 2002, 1,148 patients in England, Wales and Northern Ireland were diagnosed with candidaemia. Another estimate indicates a potential patient population of approximately 5,500 cases of invasive candidiasis or candidaemia in the UK⁷. There are currently no infectious disease surveillance programmes in the UK specific to fungal infections.

A diagnosis of invasive candidaemia is associated with increased mortality (case fatality rate of 30-40%^{8,9}) and increased length of hospital stay (an additional 14.7 to 36.3 days¹⁰), most of which is often spent in high dependency or intensive care units⁸. With early diagnosis and optimisation of therapy, it is estimated that as many as 66% of deaths could be prevented⁷. There were only 3 specialised laboratories for the diagnosis of fungal diseases in England in 2004.

Existing comparators and treatments

For invasive candidiasis, the following treatment options are available¹¹:

- **Amphotericin B (iv infusion)** – for all *Candida spp.* This drug is associated with renal impairment, therefore alternative lipid-based preparations are available (AmBisome, Abelcet and Amphocil) with reduced risk of this toxicity, but which are more expensive.

- **Fluconazole (oral or iv)** - for *Candida albicans*, particularly in AIDS patients. Both formulations can be used for invasive candidiasis. Widespread use has led to resistant strains
- **Voriconazole (oral or iv)** - licensed for fluconazole-resistant *Candida Spp.* (including *C. Krusei*)
- **Caspofungin (iv)** – use is restricted to fluconazole-resistant *Candida* infections unresponsive to amphotericin, or in patients intolerant of amphotericin.
- **Flucytosine (iv) and Amphotericin B (iv)** – used in combination for refractory cases (dose-adjustment required in renal dysfunction).

Treatment at an early stage usually leads to complete cure, however 5-10% of patients have complications such as unilateral or bilateral blindness, bone infections or surgical complications related to treatment⁷.

Efficacy and safety

Trial name or code	Dose ranging ¹²	Anidulafungin (ADF) vs fluconazole (FCZ) ¹³	Anidulafungin vs fluconazole ¹⁴
Sponsor	Vicuron Pharmaceuticals ^a	Vicuron Pharmaceuticals	National Cancer Institute
Status	Published	Abstract	Ongoing – study completed
Location	USA	Multicentre	Multi-national
Design	Phase II, randomised, open-label.	Phase III, randomised, double blind, active-comparator.	Phase III, double blind, randomised, non-inferiority.
Participants in trial	n=123 enrolled and 120 randomised (n=83 evaluable at end of treatment; n=68 at follow-up) Randomised to anidulafungin (ADF) 50, 75 or 100mg once daily. Treatment continued for 2 weeks beyond resolution or improvement of symptoms.	n=256 enrolled; n= 174 completed 6 weeks. Arm 1 (n=127): iv ADF (200mg loading dose/100mg daily maintenance dose) Arm 2 (n=118): iv FCZ (800mg loading dose/400mg daily maintenance dose) for 14-24 days. Patients transferred to oral FCZ following at least 10 days iv therapy and negative blood culture.	n=248 (expected total enrollment) Patients 16 and over. Arm 1: iv ADF (200mg loading dose/100mg daily maintenance) Arm 2: iv FCZ (800mg loading dose/400mg daily maintenance) Treatment for 10-42 days depending on severity of infection. After 10 days, patients FCZ.
Follow-up	End of treatment, then 2 week post treatment	End of treatment, then 2 and 6 weeks post treatment	Unknown
Primary outcome	Global response rate i.e. clinical and microbiologic success at 2 week follow up; <u>Clinical success:</u> defined as ‘cure’ (resolution of symptoms and no need for additional antifungal therapy) or	Global response rate at end of therapy i.e. clinical and microbiologic success – as defined previously	Effectiveness compared to fluconazole

^a Vicuron has since been acquired by Pfizer Ltd

	<p>'improvement' (significant improvement of signs and need for additional antifungal therapy);</p> <p><u>Microbiological success:</u> defined as a 'proven eradication' (negative culture from a normally sterile site that was previously positive), or 'presumed eradication' (inability to obtain cultures in a patient with a clinically successful response).</p>		
Secondary outcome	Global response rate at end of therapy and at follow up.	Global response rate at 2 weeks and 6 weeks post treatment.	Safety and prevention of late <i>Candida</i> infections.
Expected reporting date	N/A	N/A	Unknown
Key results	All species of <i>Candida</i> responded to ADF. Global response rate at 2 weeks: 72% (50mg dose); 85% (75mg dose); 83% (100mg dose)	<p><u>End of therapy</u></p> <p>ADF superior to FCZ. Response 75.6% vs 60.2% (95% CI of difference 3.9-27 p=0.01)</p> <p><u>2 weeks</u></p> <p>64.6% ADF; 49.2% FCZ (95% CI 3.1-27.7)</p> <p><u>6 weeks</u></p> <p>56% ADF; 44% FCZ (95% CI -0.6-24.3)</p>	N/A
Major adverse effects	Majority of withdrawals due to 33 deaths. Overall, 46% experienced at least one serious adverse event. Only 3 reported as possibly related to treatment: a non-fatal, non-neutropenic fever and 2 seizures in patients with complicated comorbidities.	<p>All cause mortality: ADF 22.8% vs FCZ 31.4%. All cause mortality during study therapy (7.9% vs 14.4%). Mortality attributed to <i>Candida</i> (1.6% vs 4.2%). Adverse events similar in both arms, and included histamine-mediated symptoms; diarrhoea; hypokalaemia; headache; rash; nausea; neutropeania, liver function test abnormalities.</p> <p>Discontinuation due to adverse events (ADF = 9.2%; FCZ = 16.8%)</p>	N/A

Estimated cost and cost impact

The cost of anidulafungin has yet to be finalised. AmBiosome may be the most comparable with anidulafungin on the basis it is used where nephrotoxicity precludes the use of conventional amphotericin.

Anti-fungal	Route	Dose	Cost/day ^b
Caspofungin (MSD)	iv	50mg/day maintenance	£330
Amphotericin (Squibb)	iv	1mg/kg/day	£4
AmBiosome (Gilead)	iv	3mg/kg/day	£390
Fluconazole (Non-proprietary)	iv	200mg/day maintenance	£23
Fluconazole (Non-proprietary)	oral	200mg/day maintenance	£1

Potential or intended impact – speculative

The wider issue concerns the overall service provision for the diagnosis and treatment of fungal diseases in England and Wales. If early diagnosis and optimisation of therapy could reduce mortality to the extent suggested then a service or management guideline may be a more suitable proposal.

Patients

- | | | |
|---|---|--|
| <input checked="" type="checkbox"/> Reduced morbidity | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker or more accurate diagnosis | <input type="checkbox"/> Earlier identification of disease | <input type="checkbox"/> Other: |

Services

- | | | |
|--|---|---|
| <input type="checkbox"/> Increased use e.g. length of stay, out-patient visits | <input checked="" type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input checked="" type="checkbox"/> Decreased use e.g. shorter length of stay, reduced referrals | <input type="checkbox"/> Other: | |

Costs

- | | | |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input type="checkbox"/> New costs: | <input checked="" type="checkbox"/> Savings: If it reduces hospital length of stay or use in ITU | <input type="checkbox"/> Other: |

References

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- ⁶ Lamagni TL, Evans BG, Shigematsu M et al. Emerging trends in the epidemiology of invasive mycoses in England and Wales (1990-9). *Epidemiol Infect.* 2001; 126: 397-414.

^b Costs based on British National Formulary, Number 52 (September 2006). Average patient weight of 67.5kg.

- ⁷ Health Protection Agency. Fungal diseases in the UK – The current provision of support for diagnosis and treatment: assessment and proposed network solution. Report of a working group of the HPA Advisory Committee for Fungal Infection and Superficial Parasites. London. Health Protection Agency, April 2006.
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