Scottish Medicines Consortium

voriconazole 50mg, 200mg tablets, 40mg/ml oral suspension, 200mg vials for infusion (Vfend®) No. (194/05)

Pfizer Limited

New Indication: treatment of candidaemia in non-neutropenic patients

8 July 2005

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

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Voriconazole 50mg, 200mg tablets, 40mg/ml suspension, 200mg vials (Vfend®)

Licensed indication under review Treatment of candidaemia in non-neutropenic patients

Dosing information under review Adult doses;
IV: 6mg/kg every 12 hours (for the first 24 hours) then 4 mg/kg every 12 hours.
Oral: ≥ 40kg: 400 mg every 12 hours (for the first 24 hours) then 200mg twice daily
Oral: < 40kg: 200 mg every 12 hours (for the first 24 hours) then 100mg twice daily

UK launch date
July 2005

Comparator medications

Amphocil®, Fungizone®, Ambisome® and caspofungin are indicated for the treatment of disseminated candidiasis. Abelcet® is indicated for the treatment of severe invasive candidiasis, caspofungin for invasive candidiasis and fluconazole is indicated for the treatment of systemic candidiasis including candidaemia. Amphotericin B, fluconazole and caspofungin have been recommended in the *Guidelines for Treatment of Candidiasis* produced on behalf of the Infectious Diseases Society of America, for the primary treatment of non-neutropenic candidaema.

Cost per treatment period and relevant comparators

Drug	***Dose***	***Cost per day (£)*** ***based on a 65kg patient and whole vials (where applicable)***
Voriconazole IV	**6mg/kg 12 hourly on day 1**	**463**
	4mg/kg 12 hourly maintenance dose	**309**
Voriconazole oral (tablet/suspension)	**400mg twice daily on day 1**	**143**
	200mg twice daily maintenance dose	**72**
Amphotericin B liposomal	3mg/kg/day IV (Ambisome)	692
	3-4mg/kg/day IV (Amphocil)	484-570
	5mg/kg/day IV (Abelcet)	329
Caspofungin	70mg IV on day 1	417
	50mg IV daily maintenance dose	328
Fluconazole (non -proprietary except oral suspension)	400mg IV on day 1	59
	200-400mg IV daily maintenance dose	29-59
	200-400mg oral daily maintenance dose capsule	7-14
	200-400mg oral daily maintenance dose suspension (Diflucan)	9-19
Amphotericin B conventional	1mg/kg/day IV	7

Prices taken from eVadis drug dictionary, NHS National Services Scotland (02/05/05)

Summary of evidence on comparative efficacy

Voriconazole is a broad spectrum antifungal with potent in vitro activity against *Aspergillus spp, Candida spp* (including fluconazole resistant strains of *C.albicans* and as well as other *Candida spp.* which are less sensitive to fluconazole) and *Cryptococcus spp.*

One randomised, open-label, comparative multi-centre study compared voriconazole with a regimen of conventional amphotericin B followed by fluconazole (cAMB/Flu) for the primary treatment of non-neutropenic patients with candidaemia. Patients ≥ 12 years with at least one positive blood culture for *Candida* with clinical evidence of infection were randomised in a 2:1 ratio to voriconazole or amphotericin B followed by fluconazole (cAMB/Flu). Exclusion criteria included patients with severe renal impairment (serum creatinine > 2.5mg/dl), patients with moderate or severe liver disease and patients who had failed previous systemic antifungal therapy.

The voriconazole treatment regimen comprised 6mg/kg 12 hourly on day 1, followed by 3mg/kg 12 hourly (IV dose) with an opportunity to change to oral treatment at a dose of 200mg twice daily (patients ≥ 40kg). The cAMB/Flu treatment regimen comprised amphotericin B, 0.7-1.0mg/kg/day for at least 3 days followed by fluconazole 400mg/daily oral or IV. Patients could be changed to oral administration after 3 days of IV treatment. Treatment continued for 14 days after resolution of candidaemia, and for up to 8 weeks.

The primary analysis for efficacy was the proportion of patients with a successful response to treatment, defined as cure or improvement of the infection, (as assessed by the blinded Data Review Committee) at 12 weeks after the end of treatment. Secondary analysis included the proportion of patients with a successful response at the latest relevant time-point (end of treatment, or 2, 6, or 12 weeks after end of treatment) and the Kaplan Meier survival rate at day 98.

The modified intention-to-treat population comprised 370 patients with ≥ 1 blood culture for *Candida* within 96 hours of entry and who received at least one dose of randomised study drug. Non-albicans *Candida* infected patients comprised 61% and 50% of the voriconazole and cAMB/Flu groups respectively. The median length of treatment was 15 days for both groups, and the median length of treatment with cAMB was 4 days. The proportions of patients with a successful outcome at 12 weeks after the end of treatment were 41% and 41% for both the voriconazole and cAMB/Flu groups. The proportions of patients with a successful response at the latest relevant time-point were 65% and 71% for the voriconazole and cAMB/Flu groups respectively. The Kaplan-Meier survival rates at day 98 were 63% for voriconazole and 58% for cAMB/Flu.

Summary of evidence on comparative safety

The summary of product characteristics for voriconazole details undesirable effects, reported in patients receiving voriconazole, from an integrated data base of more than 2000 patients, including 561 patients with a treatment duration exceeding 12 weeks. Very common adverse effects include; fever, headache, abdominal pain, nausea diarrhoea and vomiting, peripheral oedema, rash, and visual disturbances. The mechanism of action of visual disturbances is unknown, and was experienced by approximately 30% of patients recruited to short and long-term clinical trials. The visual disturbances are transient and fully reversible.

Voriconazole is metabolised by, and inhibits, the activity of a range of cytochrome P450 enzymes, resulting in interactions with a variety of drugs, including some combinations which

are contraindicated. A comprehensive list is available in the summary of product characteristics for voriconazole.

Summary of clinical effectiveness issues

The intravenous maintenance dose (from day 2 onwards) in the clinical study was 3mg/kg twice daily which is inconsistent with the maintenance dose, listed in the summary of product characteristics (SPC), of 4mg/kg twice daily. The SPC states that the dose can be reduced to 3mg/kg twice daily if patients are unable to tolerate treatment at 4 mg/kg twice daily.

The clinical study to support the new indication compared voriconazole with conventional amphotericin B followed by fluconazole for the primary treatment of non-neutropenic candidaemia. There is disparity between this and a statement in the submission which indicates that voriconazole is to be considered as second line treatment in patients with an infection which is fluconazole resistant or refractory to fluconazole.

Summary of comparative health economic evidence

A cost minimisation analysis was provided which compared the use of voriconazole with amphotericin B treatment for patients resistant or refractory to fluconazole therapy. The analysis was based on a patient weighing 65kg and the resource use in terms of dosing, length of treatment and associated hospital stays were taken from the open label clinical trial. The results indicated that the use of voriconazole was associated with a cost (drug acquisition and inpatient stay) of £20870 compared to £22306 with amphotericin B i.e. voriconazole was preferred on cost-minimisation grounds given its saving of £1436 per patient. The result was cost-saving in favour of voriconazole due to reductions in inpatient stays (in particular ICU bed days) offsetting the additional drug cost of voriconazole.

The cost minimisation analysis, however, had some weaknesses in its use of the clinical trial data, patient weight, the lower maintenance dose schedule and the assumed preparation in pharmacy. The company was asked to provide additional analysis using a 4mg/kg maintenance dose, assuming the voriconazole infusions were being prepared on the ward, and a patient weight of 75 kg. This analysis indicated that voriconazole would no longer be preferred on cost-minimisation grounds to amphotericin; treatment with voriconazole was indeed £193 more expensive. However, expert advice supports the need for treatment options for patients with 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.

Budget impact

The manufacturer estimated a drug budget impact per year for the next five years based on a patient weight of 65kg, a maintenance dose of IV voriconazole of 3mg/kg and assumed that part-used vials could be shared for the preparation of the two infusions per day, in a pharmacy aseptic unit. Budget impact was estimated at £73,000 for 51 patients. However a revised budget impact figures were requested from the manufacturer assuming a 75kg patient, 4mg/kg maintenance dosing and ward preparation of voriconazole. Assuming a patient population of 51 patients per year, the drug budget impact was estimated to be £191,000 per year over the next five years. If however only 5 - 10 patients were to receive voriconazole the drug budget impact would fall to £18,700 - £37,500 per year.

Guidelines and protocols

The Infectious Diseases Society of America developed and published the *Guidelines for Treatment of Candidiasis* in January 2004. Primary options for the treatment of candidaemia in non-neutropenic patients are amphotericin B, fluconazole and caspofungin. The criteria specified for consideration of an antifungal include clinical status of the patient, previous exposure to antifungal agents, knowledge of the species and/or antifungal susceptibility. The treatment duration should be for 14 days after the last positive blood culture and resolution of signs and symptoms. The guideline states that amphotericin B is preferred for infections involving *C. krusei*; however, voriconazole is cited as an alternative.

Additional information

Following a full submission, voriconazole (tablets and injection) were accepted for restricted use by the SMC in January 2003 for suspected or confirmed cases of invasive aspergillosis, infections caused by *Fusarium spp* and *Scedosporium spp* or serious invasive candidiasis refractory to fluconazole. Following an abbreviated submission, the oral suspension formulation of voriconazole was accepted for restricted use for the same indications.

In January 2004, following a full submission, caspofungin was accepted for restricted use, by the SMC for the treatment of invasive candidiasis. Its use was restricted to patients with fluconazole resistant *Candida* infection who are not responding to, or cannot tolerate amphotericin B therapy or who are at an increased risk of serious side effects with amphotericin. In addition, in December 2004 following a full submission, caspofungin was accepted for restricted use as empirical therapy for presumed fungal infections in febrile, neutropenic adult patients.

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 June 2005.***

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

1. *Pappas P, Rex J, Sobel J, Filler S, et al. Guidelines for Treatment of Candidiasis. Clinical Infectious Diseases. 2004; 38:161–89*
2. *Kullberg B, Pappas P, Ruhnke M, Viscoli C, et al. Voriconazole compared with a strategy of amphotericin B followed by fluconazole for treatment of candidaemia in non-neutropenic patients. Presented at 14th European Congress of Clinical Microbiology and Infectious Diseases, Prague, Czech Republic, 2004. Clin Microb Infect. 2004;10 (3): 1-715*
3. *Confidential Data on File: Vfend Global Candidaemia Study Report Study 150-608.*
4. *Pfizer Limited. Vfend® (voriconazole). Summary of Product Characteristics. 9 November 2004*