posaconazole 40mg/ml oral suspension (Noxafil®) No. (256/06) Schering Plough

5 May 2006

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

Posaconazole (Noxafil®) is accepted for use for use within NHS Scotland for the treatment of adults with specific invasive fungal infections refractory to or intolerant of specified antifungal agents.

The evidence to support the licensed use of posaconazole is limited to one open-label, non-comparative study mainly in patients refractory to treatment with amphotericin.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Posaconazole 40mg/ml oral suspension (Noxafil®)

Indication

For use in the treatment of the following invasive fungal infections in adults:
- invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products.
- fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B.
- chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole.
- coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Dosing information

400mg twice daily with a meal or with 240ml of nutritional supplement. In patients who cannot tolerate a meal or nutritional supplement, the recommended dose is 200mg four times daily.

UK launch date

January 2006

Comparator medications

Posaconazole is licensed for use in patients intolerant to or with infections refractory to amphotericin / itraconazole / fluconazole therefore these agents will not be considered as relevant comparators. Caspofungin and voriconazole are the key comparators in this setting. The SMC advice for these agents is detailed in the Additional Information section.

Cost of relevant comparators

Drug	Dose	Cost/day
Posaconazole (Noxafil®)	**400mg orally twice daily or 200mg four times daily**	**£95**
Caspofungin (Cancidas®)	70mg IV on day 1 then 50mg daily maintenance dose	£417 £328
Voriconazole IV (Vfend®)	6mg/kg 12 hourly on day 1 4mg/kg 12 hourly maintenance dose	£309 <65kg £463 >65kg £309
Voriconazole oral (Vfend®)	400mg twice daily on day 1 200mg twice daily maintenance dose	£158 £79

Prices for voriconazole taken from eVadis drug dictionary, NHS National Services Scotland (1/3/06). Prices for posaconazole and caspofungin not available from eVadis and taken from MIMS March 2006.

Summary of evidence on comparative efficacy

The incidence of invasive fungal infections has increased over recent years mainly as a result of the increasing use of immunosuppression. *Candida* and *Aspergillus* are the most commonly involved pathogens but other rarer fungal infections are a growing problem. Posaconazole is a new broad-spectrum triazole antifungal which like other agents in this class inhibits the synthesis of ergosterol, the primary sterol in the fungal cell membrane.

Efficacy data to support the use of posaconazole come from the results of a phase III open-label, multi-centre, non-comparative study. These results were compared against an external control based on a retrospective review of patients' medical charts. Both treatment arms enrolled patients with proven or probable invasive fungal infection who were intolerant of, or refractory to, other antifungal therapy. Refractoriness was defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy. In the posaconazole study patients received treatment in hospital at a dose of 200mg four times daily followed by 400mg twice daily after hospital discharge for a maximum of 12 months. Those who were never hospitalised used the twice-daily dose. An external blinded data review committee reviewed eligibility and study data and determined global response. The primary endpoint was the patient's global response at the end of treatment. Responders had a complete or a partial response, defined as resolution or clinically meaningful improvement of attributable symptoms, signs and radiographic, mycological or bronchoscopic abnormalities if present at baseline.

The primary analysis was based on the modified intention-to-treat population which comprised 238 posaconazole-treated patients and 218 external control patients. At the end of treatment there were 119 responders (50%) in the posaconazole group and 96 (44%) in the control group; odds ratio of 1.75 (95% CI: 1.01, 3.02, p=0.046). Aspergillus was the most common pathogen being responsible for infection in 107/238 (45%) of posaconazole and 86/218 (39%) of control patients. Most of the patients with aspergillosis were refractory to prior therapy (88% and 79% respectively) and at least 90% of these patients had already received amphotericin treatment and 40-50% itraconazole. There were 45/107 responders (42%) with posaconazole compared to 22/86 (26%) with control therapies. The adjusted odds ratio (controlling for imbalances between the groups) was 4.06 (95% CI: 1.50, 11.04, p=0.006) while unadjusted was 2.11 (95% CI: 1.14, 3.92, p=0.018). The majority of responses were partial, with 7 and 8 complete responses in each group respectively. The Kaplan-Meier analysis suggested a significant survival benefit for posaconazole over control (p<0.001). Response rates for other pathogens compared to control are as follows: Fusarium 39% vs 50%; Chromoblastomycosis or mycetoma 82% vs 0%; Coccidioidomycosis 69% vs 43% and Cryptococcus 48% vs 58%. However, the number of patients infected with pathogens other than Aspergillus was relatively small.

Summary of evidence on comparative safety

Posaconazole was generally well tolerated in patients with invasive fungal infections. Treatment-related adverse events were reported in 38% of the 428 patients who formed the total refractory invasive fungal infection population treated with ≥800mg/day. Posaconazole would appear to have a low potential for prolonging the QT interval. Posaconazole appears to affect vision to a lesser extent than voriconazole, though the effects with both drugs are mild and fully reversible.

Posaconazole is an inhibitor of CYP3A4 and caution and/or contra-indications are recommended on concomitant use of drugs that are substrates for this isoenzyme. Many of

the other triazole antifungals also interact with drugs through other cytochrome P450 isoenzymes CYP2C19 and CYP2C9 as well as CYP3A4.

Summary of clinical effectiveness issues

The efficacy data are limited by the study's open-label non-comparative design and the comparison with a retrospectively identified control group warrants caution in interpretation. The European Public Assessment Report (EPAR) notes that the lack of a prospective randomised comparative study in patients with invasive aspergillosis limited the reliability of the assessment of the risk-benefit relationship. A prospective randomised controlled study against caspofungin in aspergillosis refractory to amphotericin or itraconazole and in patients with aspergillosis who are intolerant of these antifungal agents may be conducted to address this.

The majority of patients in the posaconazole group had received prior treatment with amphotericin. Therefore, efficacy has been demonstrated in amphotericin-refractory patients. Data also suggest that posaconazole is active in itraconazole-refractory patients. However, at present there are too few data to show activity against voriconazole- or caspofungin-resistant infections. The claim of survival benefit for posaconazole should be treated with caution and should be confirmed in controlled comparative studies.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis of posaconazole oral suspension compared to the use of voriconazole iv with a switch to oral formulation, oral voriconazole alone or caspofungin iv in the treatment of invasive aspergillosis in patients who were refractory to or intolerant of amphotericin B or itraconazole. The analysis assumed equal outcomes for each drug regimen based on the results of a systematic review and indirect comparison of the posaconazole phase III trial and published studies for the comparator products (an iv/oral voriconazole study was identified so it has been assumed the outcomes apply also to oral voriconazole alone). The global response rates for each drug in invasive aspergillosis were 42-45%. The drug acquisition costs of each drug option were compared with cost savings of over £4000 per patient estimated for the use of posaconazole compared to caspofungin iv and voriconazole iv/oral formulations. A small cost saving was estimated compared to use of voriconazole oral tablets and a small positive cost estimated compared to voriconazole oral suspension.

Despite relatively weak clinical trial design and limited evidence for the patient population of interest, the studies included in the indirect comparison had similar designs and common endpoints, so the assumption of equal outcomes appears reasonable. However, the comparison of costs is based on median duration of treatment with a very wide range for each drug. As duration of therapy is a key cost driver the use of medians makes it difficult to assess the relative costs of the treatment options. Sensitivity analysis provided by the manufacturer gave reassurance, however, that based on plausible mean treatment durations a small cost saving might result from using posaconazole rather than caspofungin.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

Only 6 patients in 2006 rising to 7 in 2010 are estimated to be eligible in Scotland for posaconazole oral solution for use as salvage therapy in the treatment of invasive aspergillosis. The manufacturer estimated budget impact for posaconazole is £32,000 in 2006 rising to £37,000 in 2010, but with cost savings (or at least approximate cost neutrality) predicted if used in patients refractory to or intolerant of amphotericin or itraconazole.

Additional information

SMC has issued the following advice on other antifungal agents:

7 March 2003: Caspofungin is not recommended for use within NHS Scotland. Efficacy and safety data provided to support the possible benefits of caspofungin in the treatment of invasive aspergillosis were extremely limited, and in the form of one small, open-label, uncontrolled study. This evidence is not considered sufficiently robust to justify a recommendation for use at present. The applicant company has since confirmed that the results of a randomised clinical trial have been published in December 2002. The SMC will provide a further recommendation on this product once an additional submission has been made and assessed.

12 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).

10 December 2004: Caspofungin is accepted for restricted use within NHS Scotland for the empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult patients. It should be restricted to patients under the care of specialists experienced in the management of fungal disease. A comparative study found that caspofungin was as effective as a lipid formulation of amphotericin in terms of overall response. In addition it was better tolerated with fewer drug-related adverse events including less nephrotoxicity and infusion-related events. It is less expensive than another formulation of liposomal amphotericin, which has a licence for empirical use.

10 January 2003: Voriconazole is accepted for restricted use within NHS Scotland. Voriconazole should be used only in suspected or confirmed cases of invasive aspergillosis; for infections caused by *Fusarium spp* and *Scedosporium spp*; or serious invasive candidiasis refractory to fluconazole. It should be administered primarily to immunocompromised patienst with progressive, possibly life-threatening infections.

13 December 2004: abbreviated submission for voriconazole oral suspension received restricted recommendation as above.

8 July 2005: Voriconazole 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 therapy or who are at an increased risk of serious side effects with amphotericin.

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 14 April 2006.

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.

Keating GM. Posaconazole. Drugs 2005; 65: 1553-1567