posaconazole 40mg/ml oral suspension (Noxafil®) No. (379/07)

Schering-Plough UK Ltd

4 May 2007

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 restricted use within NHS Scotland for prophylaxis of invasive fungal infections in immunocompromised patients. It is restricted to patients in whom there is a specific risk of *Aspergillus* infection or where fluconazole or itraconazole are not tolerated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Prophylaxis of invasive fungal infections in patients receiving remission-induction chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections.

Prophylaxis of invasive fungal infections in haematopoietic stem cell transplant recipients who are undergoing high-dose immunosupressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

Dosing information

200mg (5ml) three times daily with food

Product availability date

1 December 2006

Summary of evidence on comparative efficacy

Posaconazole is a triazole antifungal that inhibits the lanosterol 14α-demethylase (CYP51) enzyme, which catalyses an essential step in ergosterol biosynthesis.

A double-blind trial recruited allogenic haematopoietic stem cell transplant recipients aged at least 13 years who had graft-versus-host disease (GVHD) and were receiving high dose immunosuppressive therapy. They were randomised equally, with stratification to posaconazole oral suspension 200mg three times daily or fluconazole oral solid dose formulation 400mg once daily for up to 16 weeks then followed-up for an additional 8 weeks. The primary outcome was incidence of proven or probable invasive fungal infections determined by a blinded independent review committee according to the European Organisation for Research and Treatment of Cancer (EORTC) Mycosis Study Group (MSG) criteria in all randomised patients within 16 weeks after randomisation. This was 5.3% (n=16/301) and 9.0% (n=27/299) in the posaconazole and fluconazole groups, respectively. The odds ratio (95% confidence intervals (CI)) was 0.56 (0.30, 1.07), with the upper confidence interval within a pre-defined limit for non-inferiority, which was based on a 15% difference between the groups. The most common type of invasive fungal infection was *Aspergillus*: 2.3% and 7.0% in the respective groups, with an odds ratio (95% CI) of 0.31 (0.13, 0.75), indicating that posaconazole was significantly superior to fluconazole for preventing invasive fungal infections caused by *Aspergillus*. Key secondary analyses were conducted during the time that patients were on-treatment, defined as the duration of study drug treatment plus seven days. In these the incidences of proven or probable invasive fungal infections were 2.4% (n=7/291) and 7.6% (n=22/288) in the posaconazole and fluconazole groups, respectively, with an odds ratio (95% CI) of 0.30 (0.12, 0.71). The incidences of infections caused by *Aspergillus* were 1.0% and 5.9% in the respective groups, with an odds ratio (95% CI) of 0.17 (0.05, 0.57). Posaconazole was significantly superior to fluconazole for preventing all invasive fungal infections and those caused by *Aspergillus* during the on-treatment period.

An open-label evaluator-blind trial recruited patients aged ≥13 years who had neutropenia (absolute neutrophil count <0.5x10^9/L) associated with remission-induction chemotherapy for acute myeloid leukaemia (AML), first relapse of AML, or a myelodysplastic syndrome (MDS). They were randomised equally to posaconazole oral suspension 200mg three times daily or to the treatment centre's designated standard azole: either an oral suspension of fluconazole 400mg once daily or itraconazole 200mg twice daily for up to 12 weeks or until neutropenia resolved. The primary outcome was the incidence of proven or probable invasive fungal infections as determined by an independent blinded data review committee according to the EORTC MSG criteria in all randomised patients during the on-treatment phase, defined as the period that patients were receiving study drug plus seven days. This was significantly lower with posaconazole compared to standard azole therapy: 2.3% (n=7/304) vs. 8.4% (n=25/298), with a between group difference (95% CI) of -6% (-9.7%, -2.5%). The incidence of proven or probable invasive fungal infections caused by *Aspergillus* was significantly lower with posaconazole: 0.66% vs. 6.7%, with a difference (95% CI) of -6% (-9.1%, -3.1%). Key secondary analyses were conducted in the 100-day post-randomisation period. During this period the incidence of all proven or probable invasive fungal infections was significantly lower with posaconazole: 4.6% (n=14/304) vs. 11% (n=33/298), with a difference (95%CI) of -6.4% (-10.8%, -2.2%).

Clinical failure

In the first study, clinical failure rate, defined as proven or probable invasive fungal infection, death, empiric use of more than 4 days of systemic antifungal therapy or loss to follow-up, was similar in the posaconazole and fluconazole groups over 16-weeks post-randomisation, 33% (n=99/301) and 37% (n=110/299) respectively, and during the on-treatment period, 17% and 18% respectively. In the second study the clinical failure rate was numerically lower with posaconazole compared to the standard azole therapy group during 100-days post-randomisation: 52% (n=158/304) and 64% (n=191/298), respectively, and was significantly lower during the on-treatment period: 27% (n=82) vs. 42% (n=126). For the latter study a similar analysis, which also included discontinuation due to adverse effects related to study drug as a criterion for clinical failure, indicated that posaconazole was associated with significantly fewer clinical failures in the on-treatment period: 36% (n=109) vs. 46% (n=138).

Mortality

In the first study overall mortality rates in the posaconazole and fluconazole groups were similar during the period while on treatment, 7.3% (n=22/301) and 8.0% (n=24/299); during the 16-week post-randomisation period, 19% (n=58) and 20% (n=59); and over the whole study period when patients were observed for 8 weeks after the 16-week treatment period, 25% (n=76) and 28% (n=84), respectively. Over the 24-week study period in the respective groups 1.3% (n=4/301) and 4.0% (n=12/299) of patients had a death that was considered by the investigator to be related to an invasive fungal infection, with the difference between the groups of borderline significance (p=0.046). In the other study overall mortality rates in the posaconazole group and the standard azole therapy group were 14% (n=44/304) and 21% (n=64/298), respectively, during the 100-day post-randomisation period and 16% (n=49) and 22% (n=67) over the whole study period. A Kaplan-Meier analysis of time to death from any cause over the 100-day period indicated a survival advantage for the posaconazole group (p=0.04). Over the whole study period there were significantly fewer deaths considered by the investigator to be related to an invasive fungal infection in the posaconazole group: 1.6% (n=5/304) compared to 5.4% (n=16/298). In both groups mean duration of study drug treatment was <30 days and about 60% of patients received treatment during one chemotherapy cycle only (i.e. approximately <28-days' treatment). A Kaplan-Meier analysis over 30 days post-randomisation indicated no difference in mortality between treatment groups.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Common adverse effects reported with posaconazole include gastro-intestinal disorders, rash and elevated liver function tests. The adverse event profiles of posaconazole in both of the trials described previously were similar to those of the other triazole antifungal drugs, fluconazole and itraconazole, which were the comparators in these studies.

Summary of clinical effectiveness issues

Posaconazole appears to be more effective than fluconazole, which has limited activity against moulds, in preventing invasive fungal infections due to *Aspergillus*. In practice, the benefits of posaconazole relative to fluconazole may be greater than those observed in the study when it is used in clinical environments that have a high incidence of fungal infections due to *Aspergillus*.

Some Scottish clinical experts advise that there is a need for more effective prophylaxis of suspected *Aspergillus* infections and that itraconazole is a more realistic comparator than fluconazole in this clinical situation. In the second study described previously, only 20% of patients received itraconazole. Comparative efficacy data relative to itraconazole, which has a spectrum of activity that includes *Aspergillus* species, are limited by small group sizes. A subgroup analysis of the primary outcome (proven or probable invasive fungal infections during the on-treatment period) was conducted using data from centres where itraconazole was the standard therapy. The incidence of proven or probable invasive fungal infections was 4.6% (n=3/65) and 10% (n=6/58) in the posaconazole and itraconazole groups respectively, with the difference between the groups not statistically significant. However, the small sample size limits the power of this analysis to identify a significant difference.

Summary of comparative health economic evidence

The manufacturer presented an assessment of posaconazole for AML/MDS and for GVHD. In both cases a short-term deterministic model was presented based upon the relevant clinical trial results as regards rates of invasive fungal infections, death rates from invasive fungal infections, and death rates from other causes. The control arms of the two relevant trials were used as comparators: fluconazole and itraconazole for AML/MDS, within which the majority of patients received fluconazole, and fluconazole for GVHD. Subsequent to the short-term modelling of treatment, survivors passed into a longer-term Markov model of survival where general population mortality rates were adjusted for the survived condition.

Additional comparators for AML/MDS modelling were voriconazole, caspofungin and liposomal amphotericin. Additional comparators for GVHD modelling were voriconazole and caspofungin. These were assumed to have the same efficacy as the relevant trial control arm, based upon an informal literature summary, and only impacted upon costs. Resource use was drawn mainly from expert opinion, particularly with regards the cost of treating an invasive fungal infection, which was a significant component of the modelling. Quality of life values were also drawn from expert opinion, through the application of the SF-6D questionnaire.

Posaconazole was estimated to dominate other treatments within the AML/MDS modelling. The likelihood of posaconazole being cost-effective relative to the fluconazole/itraconazole control arm of the trial was relatively insensitive to appropriate changes in parameter values. However, it appears that itraconazole may have been a more appropriate comparator than the primarily fluconazole control arm of the clinical trial. There was insufficient evidence from the trial and the modelling to conclude that posaconazole would be cost-effective relative to itraconazole for prophylaxis.

The cost effectiveness of posaconazole within the GVHD modelling was less certain, the central estimate being a cost effectiveness of £27,907 per QALY relative to fluconazole, this mainly being due to the increased duration of treatment. The likelihood of posaconazole being cost effective was also quite sensitive to changes in parameter values. In common with the AML/MDS modelling it appears that itraconazole may have been a more appropriate comparator than the fluconazole control arm of the clinical trial.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Two other oral triazole antifungal drugs, fluconazole and itraconazole, are licensed in the UK for prophylaxis of fungal infection in immunocompromised patients. However, itraconazole is indicated for use when standard therapies are inappropriate and the Committee for Safety of Medicines (CSM) had advised that caution be exercised when prescribing itraconazole to patients at high risk of heart failure. Some Scottish physicians advise that voriconazole and amphotericin are administered outwith their product licences for prophylaxis of invasive fungal infection for some patients, for example for patients who cannot tolerate itraconazole.

Additional information: costs

Drug	Dose	Cost per month (£)
Posaconazole	**200mg po[a] three times daily**	**2,003**
Fluconazole	50-400mg po[a] daily	66-532
Itraconazole	2.5mg/kg po[a] twice daily	363[c]
Itraconazole	200mg po[b] once or twice daily	55-109
Fluconazole	50-400mg po[b] daily	8-35

Costs are from the eVadis database accessed on 19th February, 2007. Doses are shown for general comparison and do not imply therapeutic equivalence; po = oral administration; iv = intravenous; a = oral suspension; b = oral solid dose formulation; c = based on a patient weighing 80kg.

Additional information: budget impact

Based upon around 600 AML/MDS patients being eligible, around 30 days of prophylaxis treatment per patient and a 20% market share for posaconazole, the direct posaconazole drug cost was estimated as around £250k per year. Offsetting savings from a reduction in the use of fluconazole and itraconazole of around £50k gave an annual net direct drug cost of around £200k.

For GVHD, based upon around 60 patients being eligible, around 80 days of prophylaxis treatment per patients and a 20% market share for posaconazole, the direct posaconazole drug cost was estimated as around £69k. Offsetting savings from a reduction in the use of fluconazole of around £19k gave an annual net direct drug cost of around £50k.

As a consequence, the direct drug cost was estimated as around £320k and the net direct drug cost was estimated as around £250k.

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 16 April 2007.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

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 references, shaded in grey, are additional to information supplied with the submission.

Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007; 356: 335-47

Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356: 348-59

De Pauw BE, Donnelly JP. Prophylaxis and aspergillosis – has the principle been proven? N Engl J Med 2007; 356: 409-11.