PUBLIC SUMMARY DOCUMENT

Product: Posaconazole, oral suspension, 40 mg per mL, 105 mL, Noxafil®

Sponsor: Schering-Plough Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought an authority required listing for posaconazole for treatment of invasive fungal infections, not responsive to or intolerant of, alternative therapy, in patients 13 yrs and older.

2. Background

Posaconazole had not previously been considered by the PBAC.

3. Registration Status

Noxafil is registered by the TGA for use in the treatment of the following invasive fungal infections in patients 13 years of age or older: Invasive aspergillosis in patients intolerant of, or with disease that is refractory to, alternative therapy. Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients intolerant of, or with disease that is refractory to, alternative therapy.

4. Listing requested and PBAC's View

The submission requested an authority required listing for the treatment of patients 13 years and older with proven or probable: invasive aspergillosis or fusarosis or zyygomycosis or coccidiodomycosis or chromoblastomycosis or mycetoma, that is refractory to, or intolerant of alternative therapies that have proven efficacy against the infecting pathogen.

The PBAC' view was that there was a clinical need for posaconazole as a salvage treatment in the treatment of life-threatening fungal infections. However, the PBAC noted that posaconazole was not TGA registered for the treatment of candidiasis, and considered there was potential for use outside of the recommended restriction.

5. Clinical place for the proposed therapy

Posaconazole is a broad-spectrum oral triazole antifungal proposed as salvage therapy for severely ill and/or immunocompromised patients with invasive fungal infections, where patients have disease that is refractory to or when patients are intolerant of initial treatment with standard antifungal therapy.

6. Comparator

The submission nominated voriconazole as the major comparator. The PBAC considered other salvage therapies including caspofungin, and amphotericin B lipid complex were

also appropriate as comparators because voriconazole is unlikely to be the only drug chosen for treatment of all of the conditions listed in the indication.

7. Clinical Trials

One single arm (non-comparative) study of posaconazole treatment, one single arm study of "other salvage therapies" and 3 single arm studies of voriconazole treatment were submitted. Posaconazole and other salvage therapies were compared via a logistic regression analysis and the data were used in the economic model. No statistical analysis was performed to allow a comparison between posaconazole and voriconazole.

Trial/First author	Publication title	Publication citation
P02952/ Hachem et al.	An open, non-comparative multicenter study to evaluate efficacy and safety of posaconazole (SCH 56592) in the treatment of invasive fungal infections (IFI) refractory (R) or intolerant (I) to standard therapy (ST).	Proceedings of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17–20; Toronto (Canada). Abstract 1109.
Walsh et al.	Posaconazole for treatment of invasive aspergillosis in patients who are refractory to or intolerant of conventional therapy: an externally controlled blinded trial.	Blood 2003; 102(11 Pt 1):195a (abstract 682).
Perfect et al.,	Voriconazole treatment for less-common, emerging, or refractory fungal infections.	J Clinical Infectious Diseases 2003; 36:1122–1131.
Denning et al.,	Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis	]. Clinical Infectious Diseases 2002; 34:563–571.
Marr et al.	Combination antifungal therapy for invasive aspergillosis.	J Clinical Infectious Diseases 2004; 39:797–802.

8. Results of Trials

Significantly more patients with any pathogen and treated with posaconazole responded to therapy compared with similar patients treated with other salvage therapies. When patients with *Aspergillus* as the primary pathogen were analysed separately, treatment by posaconazole showed an improved response than similar patients treated with other salvage therapies. When the odds ratio was adjusted for prognostic variables (e.g. site of infection, age etc.) the effectiveness of posaconazole was larger. Unadjusted results suggest that, apart from *Aspergillus* as the primary pathogen, posaconazole treated patients showed no better response to treatment for all other pathogens than other salvage therapies. However, patient numbers for each of these other pathogens were small and the study was likely to be underpowered to detect any difference if one existed.

The primary outcome, global response, was also reported for voriconazole (Perfect et al. 2003, Denning et al. 2002). The study by Marr et al. 2004 did not examine global response as an outcome. A similar proportion of patients responded to therapy as in the posaconazole study for patients with any pathogen and for the subset with *Aspergillus* as primary pathogen (approximately 50% and 40% respectively).

The submission claimed that survival rates were similar between posaconazole and voriconazole treated patients. This claim was not supported by the evidence presented because the differences in the nature of the trials make any comparison between them uncertain. The results suggest that survival using posaconazole was significantly better when compared with other salvage therapies for both *Aspergillus* and all other pathogens.

Safety was not evaluated for trial P02387 (other salvage therapies) and therefore a comparison (apart from deaths) could not be made between posaconazole and other salvage therapies. The number of deaths due to adverse events was higher in the posaconazole study than in the other salvage therapies study. However, only three of the 46 deaths were determined to be attributable to posaconazole.

The submission claimed that compared with voriconazole, posaconazole showed a similar number of adverse events.

9. Clinical Claim

The submission described posaconazole as having "significant clinical advantages over the main comparator" (voriconazole) because "it has similar effectiveness to the main comparator but has slightly less or similar toxicity".

Based on adjusted (logistic regression) and unadjusted analysis, the PBAC considered posaconazole was effective in salvage treatment for invasive aspergillosis and other invasive fungal infections (IFI) in adults, and more effective than other salvage therapies.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-minimisation approach was not valid based on the evidence presented.

The submission also presented a cost-effectiveness analysis comparing posaconazole (P00041) with other salvage therapies (P02387). This was acceptable as a statistical analysis was performed to adjust for potential confounding variables. The resources included were drug costs, proportion of responders and survival rates.

The trial-based incremental cost per extra responder was > $200,000 for aspergillus and for all pathogens.

A modelled economic evaluation was presented. The choice of the cost-effectiveness approach against other salvage therapies was considered valid. The outcome was survival over a two year time horizon. The resources included drug costs and survival rates. Two scenarios were tested:

In scenario 1 for patients with aspergillus as the primary pathogen, treatment with posaconazole would cost an extra $15,000 - $45,000 per life year saved compared with treatment of other salvage therapies over a period of 2 years. For scenario 2, where the survival rates of the two treatments converge, the cost per life year saved increases to $15,000 - $45,000. Where all pathogens are treated with posaconazole under the

conditions of scenario 1, the benefit is reduced with an incremental cost per life year saved of almost $45,000 - $75,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was <10,000 in Year 3 of listing, while the financial cost/year to the PBS was < $10 million in Year 3. The estimates were based on an average of 15 packs per patient per year and do not account for continued treatment in partial responders (i.e. it assumes total response).

12. Recommendation and Reasons

The PBAC recommended the listing of posaconazole on the grounds of high but acceptable cost-effectiveness compared to a suite of salvage therapies.

The PBAC accepted there is a clinical need for posaconazole as a salvage treatment in the treatment of life-threatening fungal infections. The PBAC noted posaconazole was not TGA registered for the treatment of candidiasis, and considered there was potential for use outside of the recommended restriction. There was also uncertainty associated with the incremental cost-effectiveness ratio. Therefore, the PBAC recommended that a price volume agreement be implemented.

The PBAC did not support listing on a cost-minimisation basis against voriconazole as the data are from single arm studies in which there are differences in the nature of the trials and no statistical analysis was conducted to account for possible confounding variables, and thus non-inferiority could not be excluded.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation
Posaconazole, oral suspension, 40 mg per mL, 105 mL
Restriction: Authority Required
Treatment of invasive aspergillosis in patients in patients 13 years or older intolerant to, or with disease refractory to, amphotericin B or itraconazole;
Treatment of fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis and mycetoma in patients 13 years or older intolerant to, or with disease refractory to other therapy.
Maximum quantity: 1
Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment