PUBLIC SUMMARY DOCUMENT
Product: Posaconazole, oral suspension, 40 mg per mL, 105 mL, Noxafil®
Sponsor: Schering-Plough Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought an extension to the recommended listing for the prophylaxis of invasive fungal infections (IFIs) among patients, 13 years of age or older, who are at high risk of developing these infections. The submission was considered as a Section 100 (Highly Specialised Drug) listing.

Highly specialised drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

At the July 2006 meeting, the PBAC recommended the Section 85 Authority Required listing of posaconazole on the grounds of high but acceptable cost-effectiveness compared to a suite of salvage therapies. The PBAC recommended listing for:

(a) Treatment of invasive aspergillosis in patients 13 years or older intolerant to, or with disease refractory to, amphotericin B or itraconazole; and
(b) Treatment of fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis and mycetoma in patients 13 years or older intolerant to, or with disease refractory to other therapy.

The recommendation has not been implemented due to financial considerations.

A separate submission was presented to the March 2008 meeting which provided revised economic and financial estimates for consideration by the PBAC.

3. Registration Status

Posaconazole oral suspension was registered by the TGA on 15 March 2006 and is indicated 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.

Posaconazole oral suspension is also indicated for:

- Treatment of oropharyngeal candidiasis in immunocompromised adults, including patients with disease that is refractory to itraconazole and fluconazole;
- Prophylaxis of invasive fungal infections, among patients 13 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

4. Listing Requested and PBAC's View

Authority required

For prophylaxis of invasive fungal infections, including both yeasts and moulds, among patients, 13 years of age and older, who are at high risk of developing these infections, defined as follows:

1. Neutropenia

Patients with anticipated neutropenia (an absolute neutrophil count of less than 500 cells/mm^3) for at least 10 days, such as those who are receiving chemotherapy for acute leukaemia or myelodysplastic syndrome.

Treatment should continue until recovery of the neutrophil count to at least 500 cells/mm^3.

Patients who have had a previous invasive fungal infection should have secondary prophylaxis during subsequent episodes of neutropenia.

2. Haematopoietic stem cell transplantation (HSCT), graft versus host disease (GVHD) or high risk lung transplant recipients

Patients receiving allogeneic HSCT, commencing from the day of transplantation and continuing until day 75 or until the end of immunosuppression.

Patients with acute GVHD grades II–IV or extensive chronic GVHD, who are receiving immunosuppressive therapy.

Lung transplant recipients with any of the following risk factors: airway specimen cultures positive for Aspergillus or Candida, increased immunosuppression (eg treatment with lymphocyte depleting agents or corticosteroids), cytomegalovirus (CMV) infection or obliterative bronchiolitis.

3. High risk autologous HSCT, liver or pancreatic transplant recipients or patients receiving treatment with high dose corticosteroids

Autologous HSCT recipients with lymphoma or leukaemia who have or will have prolonged neutropenia and mucosal damage from intense conditioning regimens or graft manipulation, or who have recently received fludarabine or cladribine.

Liver transplant recipients with any of the following risk factors: fulminant hepatic failure prior to transplantation, poor allograft function particularly primary nonfunction of the allograft, retransplantation, post-transplant renal failure, post-transplant infection by CMV or human herpesvirus-6 (HHV-6), repeated operation, high intraoperative transfusion requirement or extended operation time.

Pancreatic transplant recipients with any of the following risk factors: enteric drainage procedure, pancreas after kidney transplantation, preoperative peritoneal dialysis, pancreatitis after reperfusion or pancreatic retransplantation.

Patients receiving treatment with corticosteroids at methylprednisolone equivalent of more than 2 mg/kg for at least 2 weeks or corticosteroids more than 1 mg/kg and absolute neutrophil count less than 1000 cells/mm^3 for at least 1 week.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Posaconazole would provide prophylaxis for patients aged 13 years and over who are at high risk of developing invasive fungal infections such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients thereby reducing the incidence of refractory IFIs.

6. Comparator

The submission nominated fluconazole and itraconazole as the main comparators. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented two randomised trials (316 and 1899) as key evidence, in which posaconazole 600 mg/day was compared with:

(i) fluconazole 400 mg/day in trial 316 among patients with Graft Versus Host Disease (GVHD); and

(ii) fluconazole (400 mg/day)/itraconazole (400 mg/day) in trial 1899 among patients with neutropenia with Acute Myeloblastic Leukaemia (AML) and Myelodysplastic Syndrome (MDS).

The details of the key trials are presented below.

Trial/Author	Protocol title/Publication title	Publication citation
Trial 1899 Cornely et al	Posaconazole vs Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia	N Eng J Med 2007; 356(4):348-359.
Trial 316 Ullmann et al	Posaconazole or Fluconazole for Prophylaxis in Severe Graft Versus Host Disease	N Eng J Med 2007; 356(4):335-347.

The PBAC noted that the populations in the trials did not reflect all populations for whom PBS listing was sought, such as solid organ transplants for liver, lung and pancreas.

8. Results of Trials

The primary outcome in both trials was defined as the incidence of proven or probable IFIs. The results of the trials are presented in the table below.

Results of the primary outcome (proven or probable invasive fungal infections)

Trial ID	Posaconazole n/N (%)	Fluconazole/ Itraconazole n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Trial 1899	7/304 (2.3)	25/298 (8.4)	0.27 (0.12, 0.62)	-0.06 (-0.09, -0.02)
Trial 316	16/301 (5.3)	27/299 (9.0)	0.59 (0.32, 1.07)	-0.04 (-0.08, 0.00)

In trial 1899, because the upper confidence limit for the difference in the incidence of the primary outcome was less than the non-inferiority margin (4%), the non-inferiority of posaconazole was demonstrated.

In trial 1899, the incidence of the primary outcome was significantly lower with posaconazole than in the fluconazole/itraconazole group. The trial used pooled information (fluconazole/itraconazole) to demonstrate this superiority, which may have favoured posaconazole. However, given that the incidence of proven and probable IFI with posaconazole treatment was lower than with either comparator considered separately, reporting incidence rates of 8% and 10% for fluconazole and itraconazole respectively, it is reasonable to conclude that the results of this trial are a true effect.

In trial 316, the upper confidence limit of the adjusted odds ratio was within the range for non-inferiority, which was based on a 15% difference in incidence rates of the primary outcome between study groups. On this basis, the submission demonstrated non-inferiority. In this trial, there were no statistically significant differences between the study arms in the incidence of the primary outcome.

The PBAC noted the median duration of treatment with posaconazole in trial 316 was 111 days (range 1-138 days).

The results of the two trials suggested that overall, the safety profile of posaconazole is comparable to that of fluconazole/itraconazole. However, the risk difference showed that treatment-related serious adverse events were more common in the posaconazole group. Safety data reported in the trials are presented in the tables below.

Adverse events: Trial 1899

Outcome	Posaconazole n/N (%)	Fluconazole/ itraconazole n/N (%)	Relative Risk (95% CI)	Risk Difference (95% CI)
Treatment related adverse events	102/304 (34%)	101/298 (34%)	0.99 (0.79, 1.24)	0.00 (-0.08, 0.07)
Adverse events resulting in treatment discontinuation	99/304 (32%)	120/298 (40%)	0.81 (0.65, 1.00)	-0.08 (-0.15, 0.00)
Serious adverse events	159/304 (52%)	175/298 (58%)	0.89 (0.77, 1.03)	-0.06 (-0.14, 0.02)
Treatment-related serious adverse events	19/304 (6%)	6/298 (2%)	3.10 (1.26, 7.66)	0.04 (0.01, 0.07)

Adverse events: Trial 316

Outcome	Posaconazole n/N (%)	Fluconazole n/N (%)	Relative Risk (95% CI)	Risk Difference (95% CI)
Treatment related adverse events	107/301 (35%)	115/299 (38%)	0.92 (0.75, 1.14)	-0.03 (-0.11, 0.05)
Adverse events resulting in treatment discontinuation	103/301 (34%)	114/299 (38%)	0.90 (0.73, 1.11)	-0.04 (-0.12, 0.04)
Serious adverse events	222/301 (74%)	221/299 (74%)	1.00 (0.91, 1.10)	0.00 (-0.07, 0.07)
Treatment-related serious adverse events	40/301 (13%)	29/299 (10%)	1.37 (0.87, 2.15)	0.04 (-0.02, 0.09)
Adverse event as a cause of death	74/301 (24%)	81/299 (27%)	0.91 (0.69, 1.19)	-0.03 (-0.10, 0.04)

9. Clinical Claim

The submission described prophylaxis with posaconazole in high risk patients as having significant advantages in effectiveness and comparable toxicity with respect to its comparators.

The PBAC considered posaconazole to be superior to fluconazole and itraconazole in the trial populations. However, the PBAC noted uncertainty in relation to the treatment effect applied to all patients for whom listing is sought.

10. Economic Analysis

The submission presented a trial-based and modelled economic evaluation. The PBAC considered that the choice of a cost-effectiveness approach was appropriate.

A short-term decision tree was presented based on the two key trials, i.e. trial 1899 for the neutropenia model, and trial 316 for the GVHD model. This decision tree considers the incidence rate of IFI in patients at risk of IFI, IFI-related deaths, and deaths from other causes. The control group used in the economic evaluation presented by the submission was based on the two key trials, i.e. fluconazole or itraconazole (in which the majority of patients received fluconazole) for the neutropenia model, and fluconazole for the GVHD model. The results were expressed as incremental cost per IFI avoided and demonstrated cost savings in both cases. The resources included were drug costs, and costs of hospitalisation for an IFI. It should be noted that the IFI treatment cost, which was an important component in measuring the incremental cost-effectiveness ratio, was drawn only from a single centre.

Subsequent to this decision tree, survivors enter a long-term Markov model to generate the survival beyond the trial end. The patient population in the model is identical to the population in the two key trials (1899 and 316), but is not representative of the requested patient population. Furthermore, the Markov model is based only on death from underlying causes and does not allow for the possibility of death from any other conditions.

The final results were expressed as incremental cost per life year saved and also demonstrated cost savings in both cases.

The results of the analysis demonstrated that posaconazole is dominant over (i.e. more effective than) the comparators i.e. fluconazole/itraconazole in the neutropenia model and fluconazole in the GVHD model.

The results of the sensitivity analysis show that the model was most sensitive to changes in the cost of treating an IFI.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be less than 10,000 in Year 5, with a financial cost per year to the PBS of between $10 to $30 million in Year 5. The PBAC considered this was inaccurate because of the uncertainty around the estimation of posaconazole usage.

12. Recommendation and Reasons

The PBAC recommended the listing of posaconazole on the PBS for the prophylaxis of invasive fungal infections, including both yeasts and moulds, in a patient who is at high risk of developing these infections and who meets certain criteria based on acceptable cost-effectiveness compared with fluconazole and itraconazole.

The PBAC considered that posaconazole was superior to fluconazole and itraconazole in the trial populations. However, the PBAC noted that the population in the trials did not reflect all populations for whom PBS listing is sought, such as solid organ transplants for liver, lung and pancreas. The PBAC considered that the listing should be restricted to the populations in trials 1899 and trial 316, where proven benefit was shown in patients with prolonged neutropenia and in patients with severe GVHD who are at high risk of invasive fungal infection. The PBAC considered that PBS-subsidised treatment with posaconazole in the GVHD population should be limited to 6 months based on the median duration of treatment in trial 316 of 111 days (range 1-138).

The PBAC recommended removal of the age restriction to enable access for paediatric patients noting that posaconazole is not contraindicated in children.

The PBAC accepted the cost-effectiveness analysis, although noting that uncertainty remained with the substantial hospital cost offsets claimed being reliant on highly skewed costing data based on a small sample of patients.

The Committee recommended the Government enter into a risk share agreement with the sponsor to manage the possibility of usage beyond the restriction.

The PBAC noted advice from the Highly Specialised Drugs Working Party, which did not support the inclusion of posaconazole under the HSD program.

Recommendation

POSACONAZOLE, oral suspension, 40 mg per mL, 105 mL.

Restriction:	<u>Authority required</u> Prophylaxis of invasive fungal infections, including both yeasts and moulds, in a patient who is at high risk of developing these infections, defined as follows:

(1) Neutropenia
Patients receiving chemotherapy for acute myelogenous leukaemia or myelodysplastic syndrome with neutropenia (an absolute neutrophil count of less than 500 cells/mm^3) anticipated to last at least 10 days. Treatment should continue until recovery of the neutrophil count to at least 500 cells/mm^3.

Patients who have had a previous invasive fungal infection should have secondary prophylaxis during subsequent episodes of neutropenia.

(2) Graft versus host disease (GVHD)
Patients with acute GVHD grades II–IV or extensive chronic GVHD, who are receiving intensive immunosuppressive therapy after allogeneic haematopoietic stem cell transplant.
No more than 6 months therapy per episode will be PBS-subsidised.

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

The sponsor has no comments.