PUBLIC SUMMARY DOCUMENT
Product: Maraviroc, tablet, 150 mg, 300 mg, Celsentri®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing for use in combination with other antiretrovirals for the treatment of antiretroviral experienced adult patients infected with CCR5-tropic HIV-1. 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

This drug had not previously been considered by the PBAC.

3. Registration Status

Maraviroc was TGA registered on 4 February 2008 for use in combination with other antiretroviral medicinal products for treatment-experienced adult patients infected with only CCR5-tropic HIV-1.

4. Listing Requested and PBAC's View

Section 100 – Highly Specialised Drugs Program
Private hospital authority required
In combination with other antiretrovirals, for the treatment of antiretroviral experienced adult patients infected with CCR5-tropic HIV-1.
Patients must have failed previous treatment with, or have resistance to, 3 different antiretroviral regimens, including regimens with:
(i) at least 1 non-nucleoside reverse transcriptase inhibitor; and
(ii) at least 1 nucleoside reverse transcriptase inhibitor; and
(iii) at least 2 protease inhibitors.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Due to multi-class resistance, toxicity to existing classes or both, there are few options for heavily treatment experienced HIV-1 patients. Typically, standard medical management consists of three to six different antiretroviral therapies (e.g. nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors) and those which are restricted for use in salvage patients (e.g. darunavir, tipravanir, raltegravir and enfuvirtide). According to current treatment practice it is likely that maraviroc will be used as add-on therapy to darunavir and/or tipranavir and/or raltegravir plus 1 NRTI.

6. Comparator

The submission nominated the most appropriate comparator as "placebo standard medical therapy" or, as referred to in the submission, "optimised background therapy (OBT)". The PBAC considered that this was appropriate, although noted that the lack of use of raltegravir

and darunavir in the OBT group was a limitation for the interpretability of the trial data in the Australian setting.

7. Clinical Trials

The submission presented two randomised trials (A4001027 & A4001028) comparing maraviroc 300mg dose equivalent twice daily (BD) plus OBT, 300 mg dose equivalent once daily (QD) plus OBT and placebo plus OBT in patients with antiretroviral experienced adult patients infected with CCR5-tropic HIV-1. As the QD dosage was not in line with TGA recommendations this arm was excluded from consideration in the efficacy analyses in the submission, however the safety data were presented in the submission.

One of these trials had been published at the time of submission, as follows:

Trial ID	Publication title	Publication citation
A4001027	A multi-centre, randomized, double-blind, placebo-controlled trial of a novel CCR5 antagonist, maraviroc, in combination with optimized background therapy versus optimized background therapy alone for the treatment of antiretroviral-experienced HIV-1 infected subjects.	Gulick RM et al., N Engl J Med 2008; 359(14):1429-41.
A4001028	A multi-centre, randomised, double-blind, placebo-controlled trial of a novel CCR5 antagonist, maraviroc, in combination with optimised background therapy versus optimised background therapy alone for the treatment of antiretroviral-experienced HIV-1 infected subjects.	

8. Results of Trials

Key results from the trials are summarised as follows:

Change from baseline in viral load (log_{10} copies/mL) and CD4 cell count at Week 48

Trial ID	Maraviroc BD		Placebo		Treatment Difference (Maraviroc BD – placebo)	
	N	Viral load change from baseline to Week 48 Adjusted Mean (s.e.)	N	Viral load change from baseline to Week 48 Adjusted Mean (s.e.)	Estimate	97.5 % CI
A4001027	235	-1.824 (0.094)	118	-0.803 (0.133)	-1.021	-1.385, -0.658
A4001028	191	-1.865 (0.106)	91	-0.757 (0.152)	-1.109	-1.523, -0.695
Pooled result	426	-1.841 (0.070)	209	-0.781 (0.100)	-1.060	-1.332, -0.788
Chi-squared for heterogeneity					0.12, d.f. 1; (p=0.72)	

Mean change (SD) in CD4 cell count from baseline			
	Maraviroc BD	**Placebo**	**Maraviroc BD versus placebo**
	Mean (SD)	**Mean (SD)**	**Diff (95 % CI)**
A4001027	122.4 (7.28)	54.0 (10.34)	68.4 (66.3, 70.5)
A4001028	127.8 (8.50)	69.3 (12.09)	58.5 (55.7, 61.3)
Pooled result	-	-	63.5 (53.8, 73.2)
Chi-squared for heterogeneity			31.5, d.f. = 1; (p < 0.00001)
I^2 statistic with 95 % uncertainty interval*			96.8 % (91.6 %, 98.8 %)

N = number of subjects in the treatment group in the indicated population
A negative estimate of the treatment difference indicates a benefit of maraviroc in comparison with placebo.

Proportion of patients with treatment success (viral load <400 copies/mL) (pooled result)

	Maraviroc		OBT	
	24 weeks	48 weeks	24 weeks	48 weeks
Proportion of patients with treatment success	60.8%	56.3%	27.8%	22.5%

The pooled analyses showed that the maraviroc treatment was superior in reducing viral load and increasing CD4 counts, compared with placebo. However, the high drop out rate in the placebo arm creates some residual doubts about the size of the treatment effect and comparative safety of maraviroc.

Pooled safety data analyses (maraviroc BD vs placebo) indicated that maraviroc treatment was associated with statistically significantly higher rates of all adverse events compared to OBT treatment (92.3% vs 84.7%). There were statistically significantly more instances of dose reduction or temporary discontinuation due to adverse events in the maraviroc arm (p=0.02). A higher incidence of treatment-related serious adverse events was reported in the maraviroc group (2.8%) than in the placebo group (1.0%) in the pooled analysis. No new serious adverse events were identified in extended assessment of maraviroc toxicity.

9. Clinical Claim

The submission described maraviroc as superior in terms of comparative effectiveness and inferior in terms of comparative safety, compared to OBT.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

A cost utility approach was presented to compare maraviroc plus OBT with OBT in treatment of experienced HIV patients. The Markov model assumed that patients can be in one of six health states depending on their CD4 cell count, or the absorbing state (death). Whether or not a patient transitions to another health state was determined by the CD4 cell count resulting from the change in viral load (dichotomised as yes (virological suppression, <400 copies/mL) or no (virological failure)). The time horizon in the cost-effectiveness analysis was lifetime horizon and the model was structured over 26 years. The principal outcome was quality adjusted patient survival. The key component was the OBT costs.

The discounted incremental cost-effectiveness ratio was in the range of $15,000 – $45,000 per QALY.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be up to < 10,000 per year, while the financial cost per year to the PBS was estimated to < $10m in Year 5.

12. Recommendation and Reasons

The Committee agreed the proposed restriction should limit treatment to only those patients who were CCR5-tropic, as TGA registration was limited to adult patients infected with only CCR5-tropic HIV-1 detectable virus. The PBAC also considered it suitable to exclude

patients with CXCR4 tropism, as maraviroc had no activity against viruses that use CXCR4 as their co-receptor (either CXCR4-tropic or dual-tropic [infected with both CCR5- and CXCR4 strains] HIV-1 strains). Inclusion in the restriction of a viral load of greater than 5000 copies per mL was also regarded appropriate as all patients in the key trials had viral loads of at least 5000 copies per mL.

The Committee considered the comparator of placebo standard medical therapy, referred to as optimised background therapy (OBT) in the submission to be appropriate, although noting that the lack of use of raltegravir and darunavir in the OBT group was a limitation for the interpretability of the trial data in the Australian setting.

The submission presented two randomised trials (A4001027 and A4001028) comparing maraviroc 300mg dose equivalent twice daily plus OBT, 300 mg dose equivalent once daily plus OBT and placebo plus OBT in antiretroviral experienced adult patients infected with CCR5-tropic HIV-1. The once daily dosage arm was excluded from the efficacy analyses on the basis that TGA registration was only for the twice daily dosage. The PBAC accepted that the pooled analyses showed that the maraviroc treatment was superior in reducing viral load and increasing CD4 counts, compared with placebo, although the high drop out rate in the placebo arm created some residual doubts about the size of the treatment effect and comparative safety of maraviroc.

The Committee also accepted the submission's claim that maraviroc was inferior in terms of comparative safety to placebo with OBT. The pooled safety data analyses indicated that maraviroc treatment was associated with statistically significantly higher rates of all adverse events compared to OBT treatment (92.2% versus 84.7%). There were statistically significantly more instances of dose reduction or temporary discontinuation due to adverse events in the maraviroc arm and a higher incidence of treatment related serious adverse events reported in the maraviroc group (2.8%) than in the placebo group (1%) in the pooled analysis.

A major area of concern for the PBAC was the translation in the economic model of the data from the trial population to the Australian HIV population eligible under the proposed PBS listing, with the Committee considering the patients in the trials presented in the submission had more advanced disease, as indicated by CD4 cell count and viral load, compared to treatment experienced patients in Australia based on the Australian HIV Observational Database (AHOD) data. The Committee noted that the CD4 count (166.8 and 534.76) and viral load (4.85 $\log_{10}$ copies per mL and 1.77 $\log_{10}$ copies per mL) were vastly different for patients in trials A4001027 and A40011028 compared to the AHOD database patients.

Other aspects of the economic analysis increased the uncertainty in the estimated cost effectiveness of maraviroc. For example, the Markov model presented compared maraviroc plus OBT with OBT in the treatment of experienced HIV patients. The model assumed that patients can be in one of six health states depending on their CD4 cell count, or the absorbing state (death). Although CD4 count determined whether a patient transitioned to another health state (with an associated monthly probability of an adverse drug event and mortality) and drove the extrapolated ICER, the sensitivity analyses where CD4 count was adjusted had a minimal effect on the resultant ICER.

The Committee also considered that the time horizon in the economic model added to the uncertainty, as adjusting the time horizon from 26 years to ten years did not substantially change the cost per QALY gained, which was not intuitive. It was also noted that the model did not adjust for the disutility from side effects in calculating incremental QALYs, despite established inferiority for comparative safety to placebo. The utility values were modelled independent of side effects, purely on basis of CD4 count. Additionally the Committee had uncertainty in the model assumption that the CD4 count improvement with maraviroc treatment was maintained for the full 26 years time horizon of the model.

The PBAC hence rejected the application due to uncertain cost effectiveness because of issues around the translation of the trial data to the Australian HIV population and other modelling issues.

Recommendation: ***Reject***

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 notes the PBAC's view that the cost-effectiveness is uncertain and will consider its position regarding any future course of action.