PUBLIC SUMMARY DOCUMENT
Product: Maraviroc, tablets, 150 mg and 300 mg, Celsentri®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

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

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 November 2008 meeting, the PBAC rejected an application for a Section 100 (Highly Specialised Drugs Program) listing for maraviroc for treatment of antiretroviral experienced adult patients infected with CCR5-tropic HIV-1, when used in combination with other antiretrovirals on the basis of uncertain cost-effectiveness because of issues around the translation of the trial data to the Australian HIV population and other modelling issues.

Full details are available in the November 2008 Public Summary Document (PSD).

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 an antiretroviral experienced adult patient infected with only CCR5-tropic HIV-1 and:
(a) evidence of HIV replication (viral load greater than 1,000 copies per mL) and/or
(b) CD4 cell counts of less than 500 per cubic millimetre.
A patient 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.

A tropism assay to determine CCR5 only strain status is required prior to initiation. The name of the testing laboratory and date of the test are to be provided to Medicare Australia at the time of the authority application.

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, tipranavir, raltegravir and enfuvirtide). In clinical practice, maraviroc will be added to a combination of other antiretrovirals.

6. Comparator

The submission nominated standard medical management, placebo plus optimised background therapy (OBT) as the main comparator as maraviroc will be added to darunavir and/or tipranavir and/or raltegravir and/or etravirine. This was previously considered appropriate by the PBAC.

7. Clinical Trials

The trials presented (A4001027 and A4001028) have been previously reported in the November 2008 Public Summary Document.

8. Results of Trials

The results of the trials have been previously reported in the November 2008 Public Summary Document.

9. Clinical Claim

The submission described maraviroc as superior in terms of comparative effectiveness and inferior in terms of comparative safety, compared to OBT. This was previously accepted by the PBAC.

10. Economic Analysis

An updated modelled economic evaluation was presented.

The re-submission used a 1st order Monte Carlo simulation approach; patients were passed through the model one at a time, allowing the history of accumulating events to be counted using tracker variables. There were twelve Markov states: six states covered categories of CD4 cell count, and one state is death, and the AIDS Defining Events (ADE) state used in the previous model had been replaced with five Opportunistic Infection (OIs) states (viral, bacterial, fungal, protozoal and other) with the probability dependent upon CD4 category. The re-submission included tropism testing in a decision tree before patients entered the Markov model (this was not included in the previous model). The cycle length was one month, a half-cycle correction was included, and the model took a lifetime horizon.

The incremental cost per extra quality adjusted life year (QALY) gained was in the range of $45,000 to $75,000.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients per year to be less than 10,000 in Year 5 with an estimated financial cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of maraviroc tablets on the PBS in the Section 100 Highly Specialised Drugs Program for the treatment, in combination with other antiretrovirals, of antiretroviral experienced patients infected with CCR5-tropic HIV-1 who meet certain criteria on the basis of an uncertain, but acceptable, cost effectiveness ratio to optimised background therapy.

In the re-submission, an updated economic model was presented and the price of maraviroc was unchanged. The PBAC considered a number of sources of economic uncertainty remained. The PBAC noted the first order Monte Carlo simulation presented in the re-submission was again driven entirely by CD4 cell count where patients can be in one of six health states based on CD4 cell count, dead, or five opportunistic infection states (viral, bacterial, fungal, protozoal or other), and that patients transition between states depending on CD4 cell count category. The PBAC also noted that the re-submission included tropism testing in a decision tree before patients entered the model, however the PBAC considered that tropism testing should have been included in the base case. The PBAC also considered that the inability to evaluate the impact of repeat tropism testing, due to the structure of the economic model, was an additional source of uncertainty. The PBAC noted that the cost of tropism testing would not be borne by the sponsor should the test become subsidised under the Medical Benefits Schedule (MBS), and in this scenario the cost of the tropism test and frequency of testing impacts on the cost effectiveness of maraviroc. Consequently, once the test is funded under the MBS, the PBAC advised that it wished to re-examine the effect of the Government meeting this cost in a new cost-effectiveness analysis.

The PBAC noted that the economic model was very insensitive when most of the variables were adjusted. When the cost of one tropism test was included, the incremental cost per QALY was only slightly increased. The model was sensitive to the dose of maraviroc with the cost per QALY increasing when higher doses of maraviroc were used, which are recommended in the Product Information when maraviroc is used concomitantly with some antiretrovirals, due to interactions. This was deemed an important source of uncertainty considering that the economic evaluation used a maraviroc cost based on the average daily dose in the trials of 294.7 mg daily and that patients with HIV will be on a variety of different OBT regimens, leading to a substantial change in the cost of maraviroc. Similarly, the model was sensitive to a change in the cost of OBT. The model was also sensitive to the rate of viral suppression.

The PBAC noted that the lifetime horizon of the model in the re-submission remained 26 years, however that the mean life expectancy of patients in the model was less than 26 years in the maraviroc and OBT arms and considered that this was reasonable. The PBAC considered the re-submission had sufficiently addressed the uncertainty in the translation issues of the modelled HIV population to the Australian HIV population.

The PBAC noted that all costs associated with the commercial assay to determine HIV tropism, currently only available in the USA, will be funded by the sponsor. The PBAC considered that patients may receive more than one tropism assay related to their treatment with maraviroc and that the costs of any repeat testing of HIV tropism should also be borne by the sponsor. Data on the use the HIV tropism assay should be collected by the sponsor including the number of tests and repeat tests, the test results and the number of patients.

The PBAC considered that the utilisation of maraviroc was uncertain and that there is the risk of use earlier in the HIV treatment paradigm in patients with less advanced disease.

The PBAC recommended the restriction should state a viral load greater than 5,000 copies per mL for consistency with the viral loads of patients in the trials. The PBAC also considered that patients should not be allowed to be treated with maraviroc if they have demonstrated CXCR4 tropism at any time point.

Recommendation:
MARAVIROC, tablets, 150 mg and 300 mg.

Restriction: Section 100 (Highly Specialised Drugs Program)
Private hospital authority required
In combination with other antiretrovirals, for the treatment of an antiretroviral experienced patient infected with only CCR5-tropic HIV-1 and:
(a) evidence of HIV replication (viral load greater than 5,000 copies per mL) and/or
(b) CD4 cell counts of less than 500 per cubic millimetre.
A patient must have virological failure of 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.

A tropism assay to determine CCR5 only strain status is required prior to initiation. Individuals with CXCR4 tropism demonstrated at any time point are not eligible.

Pack size: 60

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

Pfizer Australia welcomes the PBAC's decision to recommend maraviroc (Celsentri®) for listing on the PBS.