PUBLIC SUMMARY DOCUMENT
Product: Etravirine, tablet, 100 mg, Intelence®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug), private hospital authority required listing for the treatment of human immunodeficiency virus (HIV) in an antiretroviral experienced patient who meets 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

This drug had not previously been considered by the PBAC.

3. Registration Status

Etravirine was TGA registered on 19 December 2008 for treatment, in combination with other antiretroviral agents, of HIV-1 infection in antiretroviral treatment-experienced adults who have evidence of viral replication and resistance to Non-nucleoside reverse Transcriptase Inhibitors and other antiretroviral agents.

4. Listing Requested and PBAC's View

Section 100 – Highly Specialised Drugs Program
Private hospital authority required
Treatment, in combination with other antiretroviral agents, of HIV infection in an antiretroviral experienced patient with:
(a) evidence of HIV replication (viral load greater than 10,000 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 which have included:
(i) at least 1 non-nucleoside reverse transcriptase inhibitor; and
(ii) at least 1 nucleoside reverse transcriptase inhibitor; and
(iii) at least 1 protease inhibitor

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Human Immunodeficiency Virus (HIV) infection is a chronic, immunosuppressive infection that is characterised by a continuous, high-level viral replication and a slow, insidious, progressive destruction of the human immune system. In the absence of effective antiretroviral treatment, HIV infection leads to severe immune deficiency and the development of the systemic opportunistic infections and cancers that define the onset of the final stage of HIV infection, the acquired immune deficiency syndrome (AIDS), and ultimately results in death.

Typically, standard medical management of HIV-1 infection consists of combinations of different antiretroviral therapies (e.g. nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)). In clinical practice, etravirine will be used in treatment experienced patients who have received 3 prior Highly Active Antiretroviral Therapy (HAART) regimens and whose current regimen is failing because of virological failure or treatment-limiting toxicity.

6. Comparator

The submission nominated placebo as the main comparator and raltegravir as an alternative comparator.

The PBAC considered that raltegravir was the most appropriate comparator given that etravirine is proposed as an alternative to raltegravir as an addition to 4th line antiretroviral therapy.

7. Clinical Trials

The following trials were presented as the basis of the submission:

a) A direct analysis of etravirine vs placebo presented as:
- two key randomised trials of etravirine + optimised background therapy (OBR) including darunavir vs placebo + OBR including darunavir (DUET 1 & 2) with pooled analysis (Pooled DUET)
- one supportive trial of etravirine + OBR vs placebo + OBR (Trial C223)

b) An indirect analysis of etravirine vs raltegravir (placebo as common comparator) presented as:
- DUET 1 & 2 (as above) with pooled analysis (Pooled DUET); compared with,
- two randomised trials of raltegravir + OBR vs placebo + OBR (BENCHMRK 1 & 2) with pooled analysis (Pooled BENCHMRK)

The trials published at the time of submission are presented below:

Trial ID/First author	Protocol title / Publication title	Publication citation
Etravirine vs placebo		
Valdez Madruga et al 2007	Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial	The Lancet 2007; 370:29-38
Lazzarin et al 2007	Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial	The Lancet 2007: 370:39-48
TMC125-C223 Writing Group 2007	Efficacy and safety of etravirine (TMC125) in patients with highly resistant HIV-1: primary 24-week analysis	AIDS 2007,21:F1-F10
Raltegravir vs placebo		
Steigbigel et al 2008	Raltegravir with optimised background therapy for resistant HIV-1 infection.	NEJM 2008; 359:339-354.
Cooper et al, 2008	Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection.	NEJM 2008; 359:355-365.

Trial ID/First author	Protocol title / Publication title	Publication citation
BENCHMRK 1 5 Sept 2007	Merck Research Laboratories Merck & Co., Inc. FDA Antiviral Drugs Advisory Committee Meeting Isentress (raltegravir) 400 mg for the treatment of HIV (NDA 22-145). Briefing Document.	http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4314b1-01-Merck.pdf.
BENCHMRK 2 5 Sept 2007	Merck Research Laboratories Merck & Co., Inc. FDA Antiviral Drugs Advisory Committee Meeting Isentress (raltegravir) 400 mg for the treatment of HIV (NDA 22-145). Briefing Document.	http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4314b1-01-Merck. pdf.

8. Results of Trials

The results of the pooled DUET trials showed that the relative risk of a virological response (plasma viral load < 50 copies/mL) with etravirine treatment compared to placebo was 1.44 (1.28, 1.61) at 24 weeks and 1.53 (1.36, 1.72) at 48 weeks.

The results of the indirect comparison of etravirine (pooled DUET trials) with raltegravir (pooled BENCHMRK trials), with placebo as the common comparator, (ITT analysis) showed a statistically significant lower effect at week 24 of etravirine treatment compared with raltegravir (in plasma viral load < 50 copies/ mL), with an indirect relative risk of 0.77 (95% CI: 0.62, 0.97), but was not statistically significant at week 48, with an indirect relative risk of 0.81 (95% CI: 0.65, 1.02).

Antiretroviral drugs used in the OBR of both trials differed, both within and between the DUET and BENCHMRK trials and differed from the intended PBS population, therefore the submission presented an indirect analysis of etravirine and raltegravir for the subgroups in both sets of trials who received darunavir (all patients in the DUET trials) but did not receive enfuvirtide (ENF) in their OBR, as this would more closely reflect the intended PBS population.

The results of the indirect comparison of etravirine with raltegravir using these subgroups, with placebo as the common comparator showed no statistically significant difference between etravirine and raltegravir in virological response at 24 and 48 weeks, but the point estimate favours etravirine rather than favouring raltegravir as in the ITT analysis. However, due to much smaller sample sizes in the subgroups analysis the 95% confidence intervals for the indirect relative risks are much wider than the indirect comparisons of the ITT groups.

No statistically significant difference was found in the comparative safety of etravirine compared with placebo, with the exception of transient rash and nausea. Etravirine was equivalent to raltegravir in terms of comparative safety. Etravirine has not yet been marketed anywhere for longer than 6 months, so no data are available on extended assessment of comparative harm.

For PBAC's comments, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that etravirine is superior in efficacy compared with placebo, with similar safety and tolerability, with the exception of transient rash and nausea. The PBAC agreed that etravirine added to OBR is superior to OBR alone at 24 and 48 weeks.

The submission also claimed that etravirine has similar efficacy and safety compared with

raltegravir, based on an indirect analysis of subgroups who received darunavir but not enfuvirtide in their optimised background regimen. The PBAC accepted this claim.

10. Economic Analysis

The submission presented a cost-minimisation analysis of etravirine compared to raltegravir based on the clinical claim of non-inferior efficacy and safety at daily doses of 400mg etravirine and 800mg raltegravir.

The submission presented a stepped economic evaluation (cost-utility analysis) comparing the costs and health outcomes for patients treated with either etravirine (plus OBR) versus OBR.

For PBAC's view, Recommendation and Reasons.

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. The estimation was considered reasonable.

The submission estimated the financial cost per year to the PBS to be less than $10 million in Year 5 of listing.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of etravirine on a cost-minimisation basis compared with raltegravir, with the equi-effective daily doses being etravirine 400 mg and raltegravir 800 mg. Listing is suitable for etravirine under section 100.

The PBAC considered that raltegravir was the most appropriate comparator given that etravirine is proposed as an alternative to raltegravir as an addition to 4th line antiretroviral therapy.

The PBAC considered the clinical trial data, based on the pooled DUET trials, demonstrated that etravirine added to OBT is superior to OBT alone at 24 weeks and 48 weeks, with the relative risk of a virological response (plasma viral load < 50 copies/mL) with etravirine treatment compared to placebo being 1.44 (1.28, 1.61) at 24 weeks and 1.53 (1.36, 1.72) at 48 weeks.

Further, the PBAC considered that the indirect comparison of relative risks of virological response for etravirine treatment versus placebo with raltegravir verus placebo (using the subgroup receiving darunavir treatment but not enfuviritide) showed no statistically significant difference between etravirine and raltegravir in virological response at 24 and 48 weeks, with the indirect relative risk point estimate slightly favouring etravirine. Hence etravirine was considered to be no worse than raltegravir based on the sub-group analysis. The Committee accepted that it was reasonable to use the subgroup analysis and also as the basis of the cost-minimisation analysis, as it more closely reflected the intended PBS population.

However, the indirect analysis of the ITT groups showed a statistically significant lower effect at week 24 week of etravirine treatment compared with raltegravir (in plasma viral load < 50 copies/ mL), with an indirect relative risk of 0.77 (95% CI: 0.62, 0.97), but was not statistically significant at week 48 with an indirect relative risk of 0.81 (95% CI: 0.65, 1.02). The PBAC agreed that the ITT analysis suggests that etravirine may be inferior to raltegravir and that uncertainty remained due to an unconfirmed understanding of why the therapeutic relativity between these two drugs varied according to which antiretrovirals (darunavir and enfuvirtide) had been tried as prior therapy.

The PBAC noted that there was no statistically significant difference in the comparative safety of etravirine compared with placebo, with the exception of transient rash and nausea and that etravirine was similar to raltegravir in terms of comparative safety.

The PBAC noted that the submission calculated the base case modelled incremental discounted cost/extra discounted QALY for etravirine plus OBR versus OBR alone to be between $45,000 - $75,000 per /QALY. The PBAC noted that the stepped economic evaluation over OBR alone is most sensitive to the magnitude of the treatment effect applied to the change in viral load over the trial period. Substituting the lower 95% confidence limit into the model increased the incremental cost per QALY gained from the base case to the highest value in the range of $75,000 - $105,000.

The PBAC noted that the calculation of PBS expenditure associated with the listing of etravirine did not take into account any substitution of raltegravir and that in clinical practice, patients may use both etravirine and raltegravir, with either of them being part of OBR at one time or another. However, the PBAC also noted that the sponsor's pre-sub-Committee response which claimed that if substitution for raltegravir occurred, the net cost to the PBS listing of etravirine would be less than that estimated.

Recommendation
ETRAVIRINE, tablet, 100 mg

Restriction: Highly Specialised Drugs Program
Private hospital authority required
Treatment, in combination with other antiretroviral agents, of HIV infection in an antiretroviral experienced patient with:
(a) evidence of HIV replication (viral load greater than 10,000 copies per mL); and/or
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(ii) at least 1 nucleoside reverse transcriptase inhibitor; and
(iii) at least 1 protease inhibitor.

Pack size: 120

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

Janssen-Cilag welcomes this decision by the PBAC to provide access to an additional treatment option for Australians living with HIV/AIDS.