PUBLIC SUMMARY DOCUMENT
Product: RALTEGRAVIR POTASSIUM, tablet 400 mg (base), Isentress®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2010

1. Purpose of Application:

The submission sought an extension to the current Section 100 (Highly Specialised Drugs Program) listing for the treatment naïve patients with human immunodeficiency virus (HIV) infection, 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:

This was the first time raltegravir had been considered by the PBAC for use in treatment naïve patients with HIV infection.

3. Registration Status:

Raltegravir was TGA registered on 28 October 2008. Raltegravir is currently registered for use in combination with other antiretroviral agents, and is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. This indication is based on analyses of plasma HIV-1 RNA levels in controlled studies of raltegravir.
The use of other active antiretroviral agents in combination with raltegravir is associated with a greater likelihood of treatment response. There are no study results demonstrating the effect of raltegravir on clinical progression of HIV-1 infection.

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 patients 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.

For PBAC's view see Recommendation and Reasons.

5. Clinical place for the proposed therapy:

Raltegravir is an integrase strand transfer inhibitor (ISTI). Raltegravir would provide an alternate treatment option for treatment naïve patients with HIV infection.

6. Comparator:

The submission nominated the comparator as a mix of non-nucleoside reverse transcriptase inhibitors (NNRTl's) efavirenz and nevirapine, and protease inhibitors (PIs) atazanavir, lopinavir and darunavir (boosted with the PI ritonavir as a pharmacokinetic enhancer). The PBAC considered that as efavirenz is the drug most likely to be replaced in practice, the comparison of raltegravir and efavirenz is the most important one.

7. Clinical trials

The submission presented two direct non-inferiority randomised trials (STARTMRK and P004) comparing raltegravir and efavirenz; and an indirect mixed treatment comparison (MCT) including three nevirapine versus efavirenz trials, one atazanavir versus efavirenz trial, two lopinavir/ritonavir versus efavirenz trials and one darunavir versus lopinavir/ritonavir trial.

STARTMRK is a multicenter, double-blind, randomized, active-controlled study which evaluated the safety and antiretroviral activity of raltegravir versus efavirenz in treatment naïve HIV-infected patients, each in combination with tenofovir disoproxil fumarate with emtricitabine. P004 is a multicenter, double-blind, randomized, dose-ranging study to compare the safety and activity of raltegravir plus tenofovir and lamivudine (3TC) versus efavirenz plus tenofovir and lamivudine (3TC) in antiretroviral therapy (ART)- naïve HIV-infected patients.

All trials were conducted in patients who were diagnosed with HIV and were naïve to antiretroviral therapy. The drugs under investigation in the trials were administered in combination with a range of optimised background therapies (OBTs).

Both of the direct randomised trials had been published at the time of submission.

Seven of the studies included in the indirect comparison published at the time of submission are as follows:

Trial ID / First author	**Protocol title / Publication title**	**Publication citation**
Direct – raltegravir vs. efavirenz		
Lennox et al 2009 (STARTMRK)	Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial.	Lennox JL, De Jesus E, et al. Lancet 374 (9692) pp796-806
Markowitz et al 2006 (P004)	Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals.	Markowitz M, Morales-Ramirez JO, et al Journal of Acquired Immune Deficiency Syndromes 43(5) pp 509-515
Markowitz et al 2007 (P004)	Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: Results of a 48-week controlled study.	Markowitz M, Nguyen B-Y, et al. Journal of Acquired Immune Deficiency Syndromes 46(2): pp 125-133
Indirect – nevirapine vs. efavirenz		
Gaytan JJA et al 2004	Nevirapine or efavirenz in combination with two nucleoside analogues in HIV-infected antiretroviral-naive patients.	Gaytan JJA, Zapata de la Garza ER, et al, Medicina Interna de Mexico, 2004; 20: 24-33
Nunez M et al 2002	SENC trial: a randomized, open-label study in HIV-infected naive individuals.	Nunez M, Soriano V, et, al, HIV Clinical Trials 2002; 3: 186-94
Van Leth F et al 2004	Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study.	Van Leth F, Phanuphak P et al, Lancet, 2004; 363: 1253-63
Indirect – atazanavir vs. efavirenz		
Squires K, et al	Comparison of once-daily atazanavir with	Squires K, Lazzarin A et

2004	efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV.	al, J Acq Immun Defic Synd 2004; 36: 1011-19
Indirect – lopinavir/ritonavir vs. efavirenz		
Riddler SA et al 2008	Class-sparing regimens for initial treatment of HIV-1 infection.	Riddler SA, Haubrich R et al, NEJM 2008; 358(20): 2095-2106
Madero J et al, 2008	A prospective, randomized, open label trial of efavirenz versus lopinavir/ritonavir based HAART among antiretroviral therapy naive HIV infected individuals presenting for care with CD4 cell counts <200mm3 in Mexico.	Madero J, Villasis A et al, AIDS 2008 XVII International AIDS Conference; 3-8 August 2008, Mexico City
Indirect (2nd degree) – darunavir vs. lopinavir/ritonavir		
Ortiz R et al 2008	Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1 infected patients at week 48.	Ortiz R, Dejesus E et al, AIDS 2008; 22(12): 1389-97

8. Results of trials

The comparison of the proportion of patients with HIV RNA less than 50 copies per mL at weeks 24, 48 and 96 in both the STARTMRK and P004 trials showed raltegravir was numerically superior to efavirenz on this outcome but the results did not reach statistical significance. The submission based its assessment of non-inferiority on the STARTMRK trial alone. At both weeks 48 and 96 the lower bound of the confidence interval was greater than -12%, which satisfied the criteria for establishing non-inferiority of raltegravir and efavirenz.

The submission provided individual trial results for the trials comparing nevirapine, atazanavir, and lopinavir/ritonavir versus efavirenz, and darunavir versus lopinavir/ritonavir. In the absence of the necessary head to head trials against nevirapine and the three PIs, the submission undertook a Mixed Treatment Comparison (MTC) based on one or more common comparators. The MTC was a Bayesian analysis using Markov chain Monte Carlo (MCMC) methods.

The submission claimed that the results of the MTC suggested that at week 48 there were statistically significant advantages for raltegravir compared to atazanavir, lopinavir/ritonavir, nevirapine and lopinavir/ritonavir plus efavirenz. However, the PBAC noted that this statistically significant advantage for raltegravir over nevirapine, atazanavir and lopinavir/ritonavir in the MTC did not concur with the individual trial evidence presented by the submission, which indicated no statistically significant differences between nevirapine, atazanavir or lopinavir/ritonavir and efavirenz.

The submission also provided results for ranking of treatment based on the MTC. These indicated that raltegravir had an 86.5% probability of being the best treatment at week 24 and a 70.7% probability of being the best treatment at week 48. Efavirenz, which the direct trial evidence indicated was non-inferior to raltegravir, had a 12.5% probability of being the best treatment at week 24 and a 2.7% chance at week 48. The submission claimed that the MTC ranking results indicated a clear advantage for raltegravir compared with all other drugs.
To test the stability of the MTC results, the analysis was rerun by removing the Ortiz et al 2008[1] trial from the analysis, as darunavir is not PBS listed for treatment naïve patients.

[1] Ortiz R, Dejesus E, Khanlou H et al, *Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1 infected patients at week 48,* AIDS, 2008; 22(12): 1389-97

(The Ortiz trial constituted 689 treatment naïve patients randomised to either darunavir/ritonavir or lopinavir/ritonavir). The revised results comparing the results presented in the submission is shown in the table below.

MTC – proportion of patients with HIV RNA less than 50 copies per mL at week 48

Trial ID	MTC – fixed effects model		
	OR Median (95% CrI)	**RD Median (95% CrI)**	**RR Median (95% CrI)**
Presented in the submission			
RAL vs RAL	1.00	0.00	1.00
RAL vs EFV	1.37 (0.89, 2.12)	0.05 (-0.02, 0.14)	1.07 (0.98, 1.21)
RAL vs. ATZ	**1.81 (1.06, 3.08)**	**0.11 (0.01, 0.23)**	**1.15 (1.01, 1.38)**
RAL vs. LPN/r	**1.86 (1.04, 3.36)**	**0.11 (0.01, 0.24)**	**1.16 (1.01, 1.42)**
RAL vs. LPN/r + EFV	**2.79 (1.49, 5.28)**	**0.21 (0.07, 0.36)**	**1.34 (1.10, 1.78)**
RAL vs. DRV	1.25 (0.62, 2.51)	0.04 (-0.07, 0.17)	1.05 (0.92, 1.27)
RAL vs. NVP	**1.74 (1.03, 2.95)**	**0.10 (0.004, 0.21)**	**1.14 (1.01, 1.35)**
Recalculated [a]			
RAL vs RAL	*1.00*	*0.00*	*1.00*
RAL vs EFV	*1.35 (0.89,2.10)*	*0.06 (-0.02, 0.16)*	*1.13 (0.97, 1.54)*
RAL vs. ATZ	***1.76 (1.02, 2.85)***	***0.10 (0.00, 0.23)***	***1.26 (1.00, 1.93)***
RAL vs. LPN/r	***2.19 (1.24, 3.62)***	***0.14 (0.02, 0.28)***	***1.40 (1.02, 2.34)***
RAL vs. LPN/r + EFV	*1.52 (0.83, 2.58)*	*0.07 (-0.03, 0.20)*	*1.17 (0.94, 1.75)*
RAL vs. NVP	***1.78 (1.03, 2.91)***	***0.10 (0.00, 0.23)***	***1.26 (1.00, 1.95)***

RAL = raltegravir; ATZ = atazanavir; EFV = efavirenz; LPN/r = lopinavir + ritonavir; NVP = nevirapine; DRV = darunavir. Values in **bold** are statistically significant.
[a] Includes exclusion of the Ortiz trial.

The PBAC noted that when the darunavir trial was removed from the MTC, raltegravir no longer had a statistical advantage over lopinavir/ritonavir plus efavirenz.

The PBAC noted that there is only limited experience to date of using a MTC approach for the purpose of an initial decision to list a drug on the PBS and that given that it is based on indirect comparisons, the results were considered less reliable than those of the head to head trials.

The PBAC noted the individual trial results for the trials comparing nevirapine, atazanavir, and lopinavir/ritonavir versus efavirenz, and darunavir versus lopinavir/ritonavir generally supported the conclusion that there were no significant differences between the other comparators and efavirenz. By inference, these trial results would suggest that raltegravir is similar in efficacy to all of the comparators, despite the results of the MTC indicating that raltegravir is superior to atazanavir, nevirapine and lopinavir/ritonavir.

The PBAC accepted that the results of the two direct non-inferiority randomised trials comparing raltegravir and efavirenz as part of first line anti-retroviral therapy indicate that raltegravir is similar in efficacy to efavirenz; and that the equi-effective doses are 800 mg raltegravir per day and 600 mg efavirenz per day.

The sponsor advised that in the pivotal STARTMRK trial, the rate of discontinuations due (only) to drug-related adverse experiences was significantly lower in the raltegravir arm

compared to the efavirenz arm (RAL, n = 3 (1.1%) versus EFV, n = 12 (4.3%); difference = -3.2% 95% CI (-6.4, -0.6), P=0.0189).

The TGA-approved Product Information states that the STARTMRK clinical trial experience found that the numbers (%) of patients with adverse experiences and with drug-related adverse experiences in the group receiving raltegravir, were less frequent than in the group receiving efavirenz. In the study, the rates of discontinuation of therapy due to adverse experiences were 3.2% in patients receiving raltegravir + emtricitabine (+) tenofovir and 6.4% in patients receiving efavirenz + emtricitabine (+) tenofovir. Drug-related clinical adverse reactions of moderate to severe intensity occurring in greater than or equal to 2% of treatment-naïve adult patients in each of the STARTMRK treatment groups included diarrhoea, nausea, fatigue, dizziness, headache, insomnia, rash including maculo papular rash.

There were statistically significantly fewer CNS related AEs in patients treated with raltegravir compared with those treated with efavirenz. The submission used this difference in the modelled evaluation and an analysis comparing the type, timing and severity of these events was provided. Efavirenz was associated with the occurrence of CNS related events including dizziness, sleep disturbance, mood swings, impaired concentration which were generally considered mild and short-term, beginning on the first or second day of the therapy and which resolved within two to four weeks.

The results of the MTC indicated significantly fewer discontinuations due to all causes for raltegravir compared with nevirapine and significantly fewer discontinuations due to adverse events or lack of efficacy for raltegravir compared with lopinavir/ritonavir. The discontinuation outcomes presented by the submission for the MTC included discontinuation due to reasons other than adverse events and it cannot be determined what proportion of discontinuations were due to adverse events and what proportion were due to other reasons. It was noted that the differences identified by the analyses might not provide an accurate picture of discontinuations due to adverse events and any potential advantages associated with raltegravir for that outcome.

The PBAC noted that during the reporting period of the Periodic Safety Update Report (PSUR) from September 2008 to March 2009, safety-related updates were made to the drug interactions, side effects and laboratory test findings sections of the Company Core Data Sheet (CCDS) for raltegravir. The side effects section was updated based on post-marketing surveillance with regard to depression and suicidal ideation and behaviours. The PSUR stated that depression, suicidal ideation and suicidal behaviours and related events are to be monitored for three years following the addition of this potential risk to the Risk Management Plan (RMP). It appeared that additional potential risks had been associated with raltegravir.

The submission claimed that the ranking of raltegravir as the best treatment in terms of discontinuation for all causes and discontinuations due to adverse events or lack of efficacy in the MTC, was a main source of safety evidence. However, the discontinuation outcomes presented by the submission allowed for discontinuation due to other reasons than adverse events and as such comparisons based on these outcomes did not directly address comparative toxicity.

The PBAC did not accept that reduced incidence of CNS adverse events were sufficient to support a claim of superiority in safety for raltegravir over efavirenz or to support a cost-effectiveness analysis. The PBAC noted that CNS toxicity with efavirenz is generally mild and usually of relatively short duration, beginning on the first or second day of the therapy and resolving within two to four weeks and can be minimised by administration at night.

9. Clinical Claim

The submission claimed raltegravir was non-inferior in terms of efficacy and superior in terms of toxicity to efavirenz; and superior in terms of efficacy and similar in terms of toxicity to atazanavir, lopinavir/ritonavir and nevirapine.

The PBAC did not consider the claim of superior efficacy and similar toxicity in comparison with nevirapine and the PIs to be reasonable as the submission claim was based on indirect comparisons, which are open to bias from a variety of sources. The PBAC noted that the individual trial results generally indicated no statistically significant differences between nevirapine, atazanavir or lopinavir/ritonavir and efavirenz. Given the direct trial evidence presented by the submission demonstrated non-inferiority of raltegravir and efavirenz, it was anticipated that an indirect comparison of raltegravir and other comparators using efavirenz as the common comparator would suggest similar efficacy between the drugs. Furthermore, the PBAC noted that it was not clear on what evidence the claim of similar toxicity of raltegravir to nevirapine, atazanavir and lopinavir/ritonavir was based. The PBAC noted that the MTC assessed discontinuations due to all causes and discontinuations due to adverse events or lack of efficacy – and that neither of these analyses assessed adverse events solely; therefore, discontinuations might be due to other events.

10. Economic Analysis

The submission presented a stepped economic evaluation using a cost-utility model. The health outcomes used in the economic model were virologic response (HIV RNA less than 50 copies per mL), CD4 cell count and CNS related adverse events.

The PBAC considered the cost-utility analysis to be inappropriate, given the direct trial evidence comparing raltegravir and efavirenz demonstrates non-inferiority between the two drugs and the indirect mixed treatment comparison does not conclusively demonstrate the superiority of raltegravir to nevirapine, atazanavir or lopinavir/ritonavir.

The PBAC noted a number of other issues raised in relation to the economic model, including uncertainties about utility decrement assigned to CNS events, the mortality rates and risk of AIDS events, the assumption used in the model that the probability of maintaining level of response across therapies beyond 96 weeks is equal to the maintenance of response seen in the last 24 week period of the trial and cost offsets.

Hence, the uncertainty in the model was reflected in the large variation of the ICER from the base case of $10,000 to $50,000 per year per quality adjusted life year (QALY) to $50,000 to $100,000 per QALY when the lower 95 % confidence limit of treatment effect is used. The PBAC also considered that modelling across all lines of therapy may not be appropriate, particularly as the treatment algorithm for HIV is rapidly evolving.

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the likely number of patients per year was estimated to be less than 10,000 treatment-naïve patients at listing date and in Year 5 and. The net financial cost per year to the PBS was estimated to be up to less than $10 million in Year 5.

Recommendation and Reasons:
The PBAC recommended the listing as a pharmaceutical benefit of raltegravir as a section 100 (Highly Specialised Drugs Program) on a cost minimisation basis compared with efavirenz. The equi-effective doses are 800 mg raltegravir per day and 600 mg efavirenz per day.

The PBAC accepted that the results of the two direct non-inferiority randomised trials comparing raltegravir and efavirenz as part of first line anti-retroviral therapy indicate that raltegravir is similar in efficacy to efavirenz. However, the PBAC did not accept that reduced incidence of CNS adverse events were sufficient to support a claim of superiority in safety for raltegravir over efavirenz or to support a cost-effectiveness analysis. The PBAC noted that CNS toxicity with efavirenz is generally mild and usually of relatively short duration, beginning on the first or second day of the therapy and resolving within two to four weeks and can be minimised by administration at night.

The PBAC noted the individual trial results for the trials comparing nevirapine, atazanavir, and lopinavir/ritonavir versus efavirenz, and darunavir versus lopinavir/ritonavir generally supported the conclusion that there were no significant differences between the other comparators and efavirenz. By inference, these trial results would suggest that raltegravir is similar in efficacy to all of the comparators, despite the results of the Mixed Treatment Comparison (MTC) indicating that raltegravir is superior to atazanavir, nevirapine and lopinavir/ritonavir.

The PBAC noted that there is only limited experience to date of using a MTC approach for the purpose of an initial decision to list a drug on the PBS and that given that it is based on indirect comparisons, the results were considered less reliable than those of the head to head trials.

The PBAC considered the cost-utility analysis to be inappropriate, given the direct trial evidence comparing raltegravir and efavirenz demonstrates non-inferiority between the two drugs and the indirect mixed treatment comparison does not conclusively demonstrate the superiority of raltegravir to nevirapine, atazanavir or lopinavir/ritonavir. Hence, the treatment effect modelled for raltegravir relative to efavirenz likely overstates the incremental effect and cost effectiveness of raltegravir. The uncertainty in the model was reflected in the large variation of the ICER from the base case in the range of $10,000 to $50,000 per year per quality adjusted life year (QALY) to a range of $50,000 to $100,000 per QALY when the lower 95 % confidence limit of treatment effect is used. The PBAC also considered that modelling across all lines of therapy may not be appropriate, particularly as the treatment algorithm for HIV is rapidly evolving.

The PBAC agreed with a number of other issues raised in relation to the economic model, including uncertainties about utility decrement assigned to CNS events, the mortality rates and risk of AIDS events, the assumption used in the model that the probability of maintaining level of response across therapies beyond 96 weeks is equal to the maintenance of response seen in the last 24 week period of the trial and cost offsets.

The PBAC noted that the price requested was based on weighting utilisation for first line therapy with current fourth line use, which was reasonable but that the price for first line therapy should be based on that for efavirenz and that the Drug Utilisation Subcommittee (DUSC) of the PBAC should monitor utilisation once listing eventuates. The PBAC also considered that the Pharmaceutical Benefits Pricing Authority should review the price following the DUSC review.

Recommendation:
RALTEGRAVIR POTASSIUM, tablet 400 mg (base)

Section 100 listing (Highly Specialised Drug)
Private hospital authority required

Treatment, in combination with other antiretroviral agents, of HIV infection in patients with:
(a) CD4 cell counts of less than 500 per cubic millimetre; or
(b) viral load of greater than 10,000 copies per mL.

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

Merck, Sharp & Dohme (Australia) Pty Ltd welcomes the PBAC decision to recommend raltegravir as an option for treatment naïve HIV patients. The Sponsor maintains that the use of an MTC is an appropriate way of assessing relative efficacy and safety of a drug versus multiple comparators in the absence of direct head to head trial evidence. The Sponsor stands by the MTC results as being consistent with the individual head to head trials.