PUBLIC SUMMARY DOCUMENT
Product: Raltegravir, tablet, 400 mg, Isentress®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

To seek a Section 100 (Highly Specialised Drug) Private hospital authority required listing for treatment, in combination with other antiretroviral agents, of human immunodeficiency virus (HIV) infection in antiretroviral experienced patients.

2. Background

This was the first time raltegravir had been considered by the PBAC.

3. Registration Status

Raltegravir was registered by the TGA on 30 January 2008 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral HIV-1 replication and HIV-1 strains resistant to multiple antiretroviral agents.

4. Listing Requested and PBAC's View

Section 100 Private Hospital Authority Required

Treatment, in combination with other antiretroviral agents, of HIV infection in antiretroviral experienced 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.

Patients 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.

See Recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Human immunodeficiency virus (HIV) infection is a chronic, immunosuppressive infection. Raltegravir would provide a new class of antiretroviral agent (HIV integrase inhibitor) as an alternative fourth-line therapy in treatment experienced patients.

6. Comparator

The submission nominated placebo as the main comparator, with darunavir as the secondary comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented three randomised, double blinded phase III trials (P005, P018/019 (BENCHMRK 1 & 2)) comparing raltegravir 400mg bid (twice daily) plus optimal background therapy (OBT) with placebo plus OBT in HIV patients, who were at least 3-class experienced.

The submission also presented an indirect comparison of raltegravir/OBT 400 mg bid vs. darunavir/control protease inhibitor (CPI) 600 mg bid, which involved raltegravir trials of P005 and P018/019, and two randomised, partially blinded, phase IIb trials (C213 & C202 (POWER 1 & 2)) comparing 600/100 mg darunavir/ritonavir (rtv) with standard care (CPI) in treatment-experienced HIV patients up to 48 weeks.

The following table lists the trials as published at the time of submission.

Trial ID	Protocol title/ Publication title	Publication citation
Raltegravir/OBT vs placebo/OBT		
P005	Grinsztejn B et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial.	*Lancet* 2007; 369 (9569):1261-1269
	Grinsztejn B et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus.	13th Conference on Retroviruses and Opportunistic Infections, February 5-8, 2006, Denver, Colorado, USA, Abstract 159LB
	Grinsztejn B et al. Potent efficacy of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus: 24-week data.	46th ICAAC - Annual International Conference on Antimicrobial Agents and Chemotherapy, September 27-30, 2006, San Francisco, California, USA, Abstract H-1670b
P018 (BENCHMRK-1) P019 (BENCHMRK-2)	Cooper D et al. Results of BENCHMRK-1, a phase III trial evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus.	14th Conference on Retrovirus and Opportunistic Infections, February 25-28, 2007, Los Angeles, California, USA, Abstract 105aLB
	Steigbigel R et al. Results of BENCHMRK-2, a phase III trial evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus.	14th Conference on Retrovirus and Opportunistic Infections, February 25-28, 2007, Los Angeles, California, USA, Abstract 105bLB
	MK518 Meta-analysis week 24 statistical report (protocol 018 and 019 combined).	15 June 2007
Darunavir/rtv vs. CPI		
C207	Arasteh K et al. TMC114/ritonavir substitution for protease inhibitor(s) in a non-suppressive antiretroviral regimen: A 14-day proof-of-principle trial.	*AIDS* 2005; 19(9):943-947
C213 (POWER-1)	Katlama C et al. Efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients: 24-Week results of POWER-1.	*AIDS* 2007; 21(4):395-402
C202 (POWER-2)	Haubrich R et al. Week 24 efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients.	*AIDS* 2007; 21(6):F11-F18
C213 & C202	Clotet B et al. Efficacy and safety of darunavir/ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER-1 and 2: a pooled subgroup analysis of data from two randomised trials.	*Lancet* 2007; 369(9568):1169-1178
C214	Madruga JV et al. Efficacy and safety of	*Lancet* 2007; 370(9581):49-58

(TITAN)	darunavir/ritonavir compared with that of lopinavir/ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial.	

8. Results of Trials

RALTEGRAVIR vs. PLACEBO (direct comparison)

There were statistically significant differences in favour of raltegravir vs. placebo for the proportion of patients with HIV RNA < 400 copies/mL, HIV RNA < 50 copies/mL, and >1 log10 drop in HIV RNA or < 400 copies/mL at both early and later time points.

The results are presented in the table below.

Percentage of patient response (NC=F analysis) across the direct randomised trials

Trial ID	Raltegravir/OBT	Placebo/OBT	Relative Risk	Risk Difference
	n with event/N(%)	n with event/N(%)	(95% CI)	(95%CI)
Percentage of patients with HIV RNA<400copies/mL (NC=F)				
P005 (24 week)	32/45 (71.1%)	7/45 (15.6%)	4.57 (2.26, 9.26)	0.56 (0.39, 0.73)
P005 (48 week)	28/44 (63.6%)	6/45 (13.3%)	4.77 (2.19, 10.39)	0.50 (0.33, 0.68)
P018/019 (16 week)	355/458 (77.3%)	99/236 (41.8%)	1.85 (1.58, 2.16)	0.36 (0.28, 0.43)
P018/019 (24 week)	347/461 (75.3%)	95/237 (40.1%)	1.88 (1.59, 2.21)	0.35 (0.28, 0.43)
Percentage of patients with HIV RNA<50copies/mL (NC=F)				
P005 (24 week)	25/45 (55.6%)	6/45 (13.3%)	4.17 (1.89, 9.16)	0.42 (0.25, 0.60)
P005 (48 week)	20/44 (45.5%)	4/45 (8.9%)	5.11 (1.90, 13.76)	0.37 (0.20, 0.53)
P018/019 (16 week)	283/458 (61.7%)	82/236 (34.7%)	1.78 (1.47, 2.15)	0.27 (0.20, 0.35)
P018/019 (24 week)	289/461 (62.7%)	80/237 (33.8%)	1.86 (1.53, 2.25)	0.29 (0.21, 0.36)
Percentage of patients with >1 log_{10} drop in HIV RNA or <400copies/mL (NC=F)				
P005 (24 week)	36/45 (80.0%)	8/45 (17.8%)	4.50 (2.36, 8.58)	0.62 (0.46, 0.78)
P005 (48 week)	29/44 (65.9%)	6/45 (13.3%)	4.94 (2.28, 10.73)	0.53 (0.35, 0.70)
P018/019 (16 week)	387/458 (84.5%)	109/236 (46.2%)	1.83 (1.59, 2.11)	0.38 (0.31, 0.45)
P018/019 (24 week)	371/461 (80.5%)	105/237 (44.3%)	1.82 (1.56, 2.11)	0.36 (0.29, 0.43)

Abbreviations: NC=F, Non-Completer = Failure.

Results from the direct comparison presented in the table below showed that patients treated with raltegravir/OBT had higher response rates and greater effects on the mean change from baseline in plasma viral RNA and CD4 cell count, compared to patients treated with placebo/OBT. However, the estimates of clinical efficacy were based on 16-24 week treatment with limited data extended to 48 weeks.

Results of Mean change from Baseline in Log_{10} HIV RNA (Log_{10} copies/mL) and in CD4 cell count (cells/mm^3) across the direct randomised trials (OF analysis)

Trial ID	Raltegravir/OBT			Placebo/OBT			Mean Difference (95% CI)
	n /N (%)	Baseline mean	Change (95% CI)	n /N (%)	Baseline mean	Change (95% CI)	Difference in mean changes from baseline
Log_{10} HIV RNA (Log_{10} copies/mL) (OF)							
P018/019 (16 wk)	446/466 (96%)	4.65	-1.89 (-1.98, -1.80)	230/237 (97%)	4.59	-0.92 (-1.06, -0.78)	-0.96* (-1.13, -0.80)
P018/019 (24 wk)	448/466 (96%)	4.65	-1.82 (-1.91, -1.72)	232/237 (98%)	4.59	-0.87 (-1.00, -0.73)	-0.95* (-1.12, -0.78)
P005 (24 wk)	45/45 (100%)	4.77	-1.87 (-2.16, -1.58)	45/45 (100%)	4.68	-0.35 (-0.61, -0.09)	-1.52* (-1.90, -1.14)
P005 (48 wk)	44 /44 (100%)	4.77	-1.55 (-1.92, -1.19)	44/45 (98%)	4.69	-0.28 (-0.50,-0.05)	-1.27* *(-1.7, -0.84)*
CD4 cell count (cells/mm^3) (OF)							
P018/019 (16 wk)	446/466 (96%)	152.6	84.4 (75.5, 93.3)	229/237 (97%)	157.8	35.6 (26.0, 45.1)	48.8 (35.8, 61.9)
P018/019 (24 wk)	437/466 (94%)	151.0	83.7 (74.9, 92.5)	229/237 (97%)	158.8	36.5 (27.0, 46.0)	47.2 (34.3, 60.1)
P005 (24 wk)	43/45 (96%)	225.1	112.8 (75.7,150.0)	43/45 (96%)	277.0	5.4 (-9.9,20.7)	107.4 (67.6, 147.3)
P005 (48 wk)	43/45 (96%)	222.5	110.1 (69.3, 150.8)	43/45 (96%)	267.1	16.8 (-0.4, 34.1)	93.3 (NC)

Notes: * negative effect sizes indicate improvement; NC= not calculated; OF=observed failure.

RALTEGRAVIR vs. DARUNAVIR (indirect comparison)

For the purpose of the indirect comparison, the submission presented data for the common endpoints for the subgroup of patients who did not use darunavir/rtv as part of their OBT (-darunavir/rtv) in P018/019.

There were no statistically significant differences between raltegravir and darunavir in the proportions of patients with HIV RNA < 400 copies/mL at 24 weeks and HIV RNA < 50 copies/mL at both 24 and 48 weeks. Results were inconsistent for mean change from baseline in CD4 count at 24 weeks. In the indirect comparison between P005 and C202, the difference in mean change in CD4 count favored raltegravir. However, the result from the indirect comparison of P018/019 vs. C213 showed that darunavir is superior to raltegravir in terms of change in CD4 count.

The results are presented in the tables below.

Results of percent of patients with HIV RNA<400copies/mL or with HIV RNA < 50copies/mL

Trial ID	Trials of Raltegravir (RTV)			Trials of Darunavir (DRV)			Ratio of RR (95% CI)
	RR (95% CI)	RTV/OBT n /N (%)	P/OBT n /N (%)	CPI/OBT n /N (%)	DRV/rtv n/N (%)	RR (95% CI)	
Percent of patients with HIV RNA<400copies/mL at week 24							
P005 vs C213	4.57 (2.26, 9.26)	32/45 (71.1%)	7/45 (15.6%)	15/60 (25%)	40/60 (66.7%)	2.67 (1.66, 4.28)	1.7 *(0.75, 4.01)*
P005 vs C202	4.57 (2.26, 9.26)	32/45 (71.1%)	7/45 (15.6%)	4/42 (9.5%)	19/39 (48.7%)	5.12 (1.91, 13.71)	0.89 *(0.27, 3.01)*
P018/019 vs C213	2.48 (1.89, 3.25)	199/271 (73.4%)	40/135 (29.6%)	15/60 (25%)	40/60 (66.7%)	2.67 (1.66, 4.28)	0.93 *(0.54, 1.60)*
P018/019 vs C202	2.48 (1.89, 3.25)	199/271 (73.4%)	40/135 (29.6%)	4/42 (9.5%)	19/39 (48.7%)	5.12 (1.91, 13.71)	0.48 *(0.17, 1.35)*
Percent of patients with HIV RNA<50copies/mL at week 24							
P005 vs C213	4.17 (1.89, 9.18)	25/45 (55.6%)	6/45 (13.3%)	11/60 (18.3%)	32/60 (53.3%)	2.91 (1.62, 5.22)	1.43 *(0.54, 3.82)*
P005 vs C202	4.17 (1.89, 9.18)	25/45 (55.6%)	6/45 (13.3%)	3/42 (7.1%)	15/39 (39%)	5.38 (1.69, 17.18)	0.77 *(0.19, 3.15)*
P018/019 vs C213	2.63 (1.92, 3.61)	169/271 (62.3%)	32/135 (23.7%)	11/60 (18.3%)	32/60 (53.3%)	2.91 (1.62, 5.22)	0.90 *(0.47, 1.76)*
P018/019 vs C202	2.63 (1.92, 3.61)	169/271 (62.3%)	32/135 (23.7%)	3/42 (7.1%)	15/39 (39%)	5.38 (1.69, 17.18)	0.49 *(0.15, 1.63)*
Percent of patients with HIV RNA<50copies/mL at week 48							
P005 vs C202/213	5.11 (1.90, 13.8)	20/44 (45.5%)	4/45 (8.9%)	12/120 (10%)	50/110 (45%)	4.55 (2.56, 8.07)	1.12 *(0.4, 3.5)*

Results of mean change from baseline in CD4 cell count at week 24 and week 48 or in viral load at week 48

Trial ID	Trials of Raltegravir (RTV)			Trials of Darunavir (DRV)			Difference between the differences (95% CI)
	Difference (95% CI)	RTV/OBT Mean change (n/N, %)	P/OBT Mean change (n/N, %)	CPI/OBT Mean change (n/N, %)	DRV/OBT Mean change (n/N, %)	Difference (95% CI)	
Mean change from baseline in CD4 cell count (cells/mm^3 or cells/µl) at week 24							
P005 vs C213	107.4 (67.6, 147.3)	112.8 (43/45, 96%)	5.4 (43/45, 96%)	20 (60/65, 92%)	124 (60/63, 95%)	104 *(81.3, 126.7)*	3.4 *(-42.5, 49.3)*
P005 vs C202	107.4 (67.6, 147.3)	112.8 (43/45, 96%)	5.4 (43/45, 96%)	12 (42/60, 70%)	59 (39/57, 68%)	47 (27.6, 68.4)	**60.4 *(16.1, 104.7)***
P018/019 vs C213	67.1 (50.4, 83.8)	86.4 (263/271,97%)	19.3 (135/135,100%)	20 (60/65, 92%)	124 (60/63, 95%)	104 *(81.3, 126.7)*	**-36.9 *(-65.1, -8.7)***
P018/019 vs C202	67.1 (50.4, 83.8)	86.4 (263/271,97%)	19.3 (135/135,100%)	12 (42/60, 70%)	59 (39/57, 68%)	47 (27.6, 68.4)	20.1 *(-5.5, 45.7)*
Mean change from baseline in CD4 cell count (cells/mm^3 or cells/µl) at week 48							
P005 vs C202/213	93.3 *(49.0, 137.6)*	110.1 (43/45, 96%)	16.8 (43/45, 96%)	19 (27/121, 22%)	102 (84/130, 65%)	83 *(69.8, 96.2)*	10.3 *(-35.9, 56.5)*
Mean change from baseline in viral load (log_{10} copies/mL) * at week 48							
P005 vs C202/213	-1.27 (NR)	-1.55 (44/44, 100%)	-0.28 (44/45, 98%)	-0.35 (NR)	-1.63 (NR)	-1.28 (NR)	0.01 *(-0.5, 0.5)*

Notes: * negative effect sizes indicate improvement; bold shows statistically significant difference.

The PBAC noted that overall although there are some differences between the baseline characteristics and OBT components of the trials, the submission's claim that raltegravir was non-inferior to darunavir/rtv based on an indirect comparison, appeared reasonable.

The safety data showed no significant differences in gastrointestinal or nervous system adverse events and in all-cause mortality and mortality for AIDS defining conditions in raltegravir/OBT patients, compared with placebo/OBT patients. A higher rate of malignancy was observed in raltegravir/OBT group.

The sponsor has undertaken to continue monitoring and reporting on the rates of malignancies. Further surveillance for malignancies will be conducted using three main approaches (routine pharmacovigilance, ongoing/planned clinical trials and active surveillance). This additional data will be provided to the TGA for evaluation on an ongoing basis.

The safety profile for raltegravir/OBT compared to placebo/OBT was based on the 16 week double-blind trial phase. Longer term toxicity of raltegravir is currently unknown. The sponsor stated that the most recent safety information for raltegravir includes data from patients who have been on raltegravir for 48 weeks. It was also noted that the safety profile of raltegravir continues to be monitored.

9. Clinical Claim

The submission described raltegravir as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

The submission described raltegravir as non-inferior to darunavir in terms of effectiveness and toxicity.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A stepped economic evaluation was presented. The model was a Monte Carlo microsimulation of a Markov model, with patients cycling through the Markov process in six month cycles. There were four health states in the model: clinical trial period of 6 month cycles, treatment with study regimen (patients with viral load < 10,000 after the clinical trial period), treatment with a salvage regimen (patients with viral load > 10,000 after the clinical trial period or virologic failure after the study regimen) and death. The time horizon in the base case was lifetime. The resources included were drug costs and costs for AIDS events. The outcomes used in the model are life years gained (LYG) and Quality-Adjusted Life Years (QALYs).

The PBAC considered the most relevant analysis to be the incremental cost-effectiveness ratios of raltegravir in comparison with OBT, including darunavir. The submission calculated an incremental cost per extra QALY gained in the range of $45,000 to $75,000, and an incremental cost per LYG in the range of $45,000 to $75,000.

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, at a financial net cost per year to the PBS of less than $10 million in Year 5.

The PBAC noted that the submission's estimate could be an underestimate given that the cost of darunavir or tipranavir had not been taken into account which results in the overestimate of

cost offsets associated with the reduction of nucleoside reverse transcriptase inhibitors (NRTIs) use.

12. Recommendation and Reasons

The PBAC recommended listing based on a high and acceptable incremental cost-effectiveness ratio compared to placebo (both added to optimal background therapy (OBT) including darunavir).

The PBAC considered the clinical trial data presented demonstrates that raltegravir added to OBT is superior to OBT alone at 24 weeks and 48 weeks, although the conclusion at 48-weeks is based on a smaller number of patients.

Further, the PBAC considered that although in the indirect comparison presented versus darunavir there were some differences between the baseline characteristics and OBT components of the trials, the submission's claim that raltegravir is non-inferior to darunavir/ritonavir was reasonable.

The PBAC notes a higher rate of malignancy was observed in raltegravir/OBT group in the clinical trials based on the 16 week double-blind trial phase and the availability of long-term safety data available is limited. The Pre-PBAC response advised that while there were imbalances in the rates of malignancies observed in the data sourced from the phase II and III studies that were submitted in the Australian regulatory submission, this was not sustained when an updated cumulative analysis of the same study cohorts was subsequently conducted. The rates of malignancies are 2.32 per 100 person years in the raltegravir arm versus 1.92 in the control arm when the full 24 week data is taken into account. Nevertheless, the sponsor undertook to continue monitoring and reporting on the rates of malignancies across both groups. Further surveillance for malignancies will be conducted using three main approaches (routine pharmacovigilance, ongoing/planned clinical trials and active surveillance). This additional data will be provided to the TGA for evaluation on an ongoing basis.

The modelled economic evaluation, which estimated the cost-effectiveness of raltegravir in comparison with OBT, including darunavir, was considered the most relevant analysis. The submission calculated an incremental cost per extra QALY gained in the range of $45,000 to $75,000, which was considered acceptable by the PBAC.

Recommendation

RALTEGRAVIR, tablet, 400 mg.

Restriction:	Section 100 (Highly Specialised Drugs Program) <u>Private Hospital Authority Required</u> 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.

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

Sponsor chose not to make a comment.