PUBLIC SUMMARY DOCUMENT
Product: Darunavir, tablets, 150 mg and 300 mg (as ethanolate), Prezista®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought an extension to the current Section 100 (Highly Specialised Drugs Program) listing to include treatment, in combination with other antiretrovirals, of human immunodeficiency virus (HIV) infection in antiretroviral experienced patients who have failed previous treatment with, or have resistance to, one antiretroviral regimen, and 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 July 2007 meeting, the PBAC recommended a Section 100 (Highly Specialised Drugs Program) listing of darunavir for the treatment of HIV infection in antiretroviral treatment experienced patients who must have failed previous treatment with, or have resistance to, three different antiretroviral regimens. This was on the basis of a high but acceptable incremental cost-effectiveness ratio compared with tipranavir. Full details are available in the July 2007 Public Summary Document.

3. Registration Status

Darunavir was first TGA registered on 15 March 2007 and was indicated for treatment of HIV-1 infection, in combination with other antiretroviral agents, in heavily pre-treated adults with evidence of viral replication, who have HIV-1 strains resistant to multiple protease inhibitors.

On 30 July 2009, the TGA registration for darunavir was changed to use (with low dose ritonavir as a pharmacokinetic enhancer) in combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 infection in adult patients.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private hospital authority required
Treatment, in combination with other antiretroviral agents, and co-administered with 100 mg ritonavir twice daily, 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, 1 antiretroviral regimen.

The PBAC had no objection to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

HIV infection is a chronic, immunosuppressive infection characterised by continuous, high-level viral replication and slow, progressive destruction of the human immune system.

Highly active antiretroviral therapy (HAART) has reduced HIV-related morbidity and mortality, and increased the life expectancy of HIV-infected individuals. HAART usually consists of combinations of different antiretroviral therapies (e.g. nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors).

The change to the current PBS listing for darunavir would allow its use earlier in the clinical management of HIV-1 infection, after failure or resistance to one antiretroviral regimen.

6. Comparator

The submission nominated lopinavir with ritonavir as the main comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented one randomised trial (TITAN) comparing darunavir 600 mg/ritonavir 100mg bd (twice daily) added to optimised background regimen with lopinavir 400 mg/ritonavir 100 mg bd added to optimised background regimen in patients with HIV that are both early treatment (prior treatment with ≤1 protease inhibitor) and treatment experienced (prior treatment with ≥ 2 protease inhibitors).

The ITT results of the TITAN study were not directly applicable to the extension of listing sought, and the submission presented a post-hoc sub-group analysis from the TITAN study of the ITT results of patients that have previously been treated with ≤ 1 protease inhibitor (PI) as more representative of the extension to listing being sought, as well as a post-hoc subgroup analysis of highly treatment experienced patients (≥ 2 PIs).

Details of the published studies presented in the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Madruga JV et al	Efficacy and safety of 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.	*Lancet* 2007: 370(9581); 49-58.
De Meyer S et al	Influence of baseline protease inhibitor resistance on the efficacy of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial.	*J Acquir Immune Defic Syndr* 2008: 49(5); 563-573
Bánhegyi D et al	Phase III TITAN Week 96 final analysis: efficacy/safety of darunavir/ritonavir versus lopinavir/ritonavir in lopinavir/ritonavir-naïve, treatment-experienced patients	Poster P22, 9th International Congress on HIV and Drug Therapy in HIV Infection, Glasgow, UK, 9–13 November 2008
De Meyer S et al	Resistance development in virological failures with DRV/r or LPV/r: 96-week analysis of the Phase III TITAN trial in treatment-experienced patients	Oral Presentation, 9th International Congress on HIV and Drug Therapy in HIV Infection, Glasgow, UK, 9–13 November 2008

8. Results of Trials

The published results of the TITAN trial are summarised in the tables below.

Primary Outcome - Virological Response < 400copies/mL

Primary outcome - proportion of patients with virological response < 400 copies/mL in TITAN

	ITT	
	Darunavir/ rtv	**Lopinavir/ rtv**
	N=298	N=297
Week 48 N (%)	228 (76.5)	199 (67.0)
Relative Risk (95% CI)	1.14 (1.03, 1.26)	
Absolute Risk Difference (95% CI)	9.5 (2.3, 16.7)	
Week 96 N (%)	199 (66.8)	175 (58.9)
Relative Risk (95% CI)	1.13 (1.001, 1.283)	
Absolute Risk Difference (95% CI)	7.9 (0.1, 15.6)	

OBR=optimised background regimen
rtv = ritonavir

The PBAC noted at 48 weeks and 96 weeks for both the ITT population and highly treatment experienced patient group (≥2 prior PIs), the relative risk and absolute risk difference in the proportion of patients with virological response <400 copies/mL were statistically significantly in favour of the darunavir/rtv arm. The results in the early treatment patients who had received ≤1 prior PI were not statistically significantly different at week 48 or week 96.

Secondary Outcome - Virological Response <50 copies/mL

Secondary outcome - proportion of patients with virological response <50 copies/mL in TITAN

	ITT	
	Darunavir/rtv	**Lopinavir/rtv**
	N=298	N=297
Week 48 N (%)	211 (70.8)	179 (60.3)
Relative Risk (95% CI)	1.17 (1.04, 1.32)	
Absolute Risk Difference (95% CI)	10.5 (2.9, 18.1)	
Week 96 N (%)	180 (60.4)	164 (55.2)
Relative Risk (95% CI)	1.09 (0.95, 1.26)	
Absolute Risk Difference (95% CI)	5.2 (-2.8, 13.1)	

The ITT results from TITAN showed that the darunavir/rtv was superior to lopinavir/rtv at Week 48 for the secondary outcome of virological response defined as viral load < 50 Copies/mL. This superiority was not maintained at Week 96 and the submission described the two drugs as being not different at Week 96. The point estimate for the proportion of patients achieving a virological response measured by < 50 copies per mL remains higher with darunavir/rtv treatment than lopinavir/rtv treatment until just after week 48. For the post hoc sub groups by prior PI treatment darunavir/rtv was superior to lopinavir/rtv in the heavily pre-treated patients (treated with ≥2 prior PIs) at both time points, Week 48 and 96. Darunavir/rtv was not different to lopinavir/rtv in the early treatment experienced patients (treated with ≤1 prior PIs) at Week 48; and Week 96.

The number of virological failures by week 96 was lower in the darunavir/rtv ITT population (41/298 – 13.8%) than the lopinavir/rtv group (76/297 – 25.6%). Proportionally fewer virological failures in the darunavir/rtv arm developed mutations than in the lopinavir/rtv arm.

Fewer virological failures treated with darunavir/rtv than with lopinavir/rtv treatment lost susceptibility to other PIs.

However, no data were provided about the efficacy of lopinavir after a patient has been treated with darunavir. The PBAC considered the movement of darunavir towards earlier treatment could impact on the overall cost and outcomes of the treatment of HIV.

For the purpose of cost-minimisation the submission assumed that there was no difference in adverse events between darunavir/rtv and lopinavir/rtv, except for the incidence and prevalence of diarrhoea.

Summary of Incidence of key AEs in TITAN (Regardless of Severity and Causality >5% incidence)

	48 Weeks			96 Weeks		
TMC114-C214 (TITAN)	**Darunavir/rtv 600/100mg bd + OBR**	**Lopinavir/rtv 400/100mg bd + OBR**	**Risk Difference (95% CI)**	**Darunavir/rtv 600/100mg bd + OBR**	**Lopinavir/rtv 400/100mg bd + OBR**	**Risk Difference (95%CI)**
N=	298	297		298	297	
Any AE n (%)	277 (93.0)	273 (91.9)	1.0 (-3.2, 5.3)	281 (94.3)	281 (94.6)	-0.3(-4.0, 3.4)
Gastrointestinal Disorders n (%)	176 (59.1)	177 (59.6)	-0.5 (-8.4, 7.4)	192 (64.4)	190 (64.0)	0.5 (-7.2, 8.2)
Diarrhoea	95 (31.9)	124 (41.8)	**-9.9 (-17.6, -2.2)**	105 (35.2)	138 (46.5)	**-11.2 (-19.1, -3.4)**
Nausea	55 (18.5)	62 (20.9)	-2.4 (-8.8, 4.0)	58 (19.5)	65 (21.9)	-2.4 (-8.9, 4.1)
Abdominal pain	29 (9.7)	21 (7.1)	2.7 (-1.8, 7.1)	35 (11.7)	24 (8.1)	3.7 (-1.1, 8.5)
Vomiting	26 (8.7)	21 (7.1)	1.7 (-2.7, 6.0)	31 (10.4)	23 (7.7)	2.7 (-2.0, 7.3)
Nervous System Disorders n (%)	82 (27.5)	50 (16.8)	**10.7 (4.1, 17.3)**	93 (31.2)	60 (20.2)	**11.0 (4.0, 18.0)**
Headache	33 (11.1)	22 (7.4)	3.7 (-1.0, 8.3)	36 (12.1)	26 (8.8)	3.3 (-1.6, 8.2)
Dizziness	14 (4.7)	10 (3.4)	1.3 (-2.2, 4.8)	17 (5.7)	13 (4.4)	1.3 (-2.1, 4.8)
Skin & Subcutaneous Tissue Disorders n (%)	94 (31.5)	72 (24.2)	**7.3 (0.1, 14.5)**	105 (35.2)	86 (29.0)	6.3 (-1.2, 13.8)
Rash	19 (6.4)	12 (4.0)	1.3 (-2.1, 4.7)	22 (7.4)	15 (5.1)	2.3 (-1.5, 6.2)
Pruritus	7 (2.3)	17 (5.7)	**-3.4 (-6.5, -0.2)**	8 (2.7)	17 (5.7)	-3.0 (-6.3, 0.2)

9. Clinical Claim

The submission claimed that darunavir is at least non-inferior to lopinavir with superior tolerability and no additional toxicity for the population for whom the extended PBS listing was requested.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis. The equi-effective doses were darunavir 600 mg/ritonavir 100 mg twice daily and lopinavir 400 mg/ritonavir 100 mg twice daily.

11. Estimated PBS Usage and Financial Implications

The estimated number of patients per year was less than 10,000 in Year 5, with estimated cost savings per year to the PBS of less than $10 million in Year 5.

The PBAC considered the submission's estimates to be uncertain due to the uncertainty associated with the estimate of the uptake rate of darunavir in early treatment experienced patients.

12. Recommendation and Reasons

The PBAC recommended that darunavir co-administered with ritonavir be listed for the treatment in combination with other antiretroviral agents for patients who have failed previous treatment with, or have resistance to, one antiretroviral treatment regimen, on a cost minimisation basis compared with lopinavir with ritonavir (Kaletra®).

The PBAC considered that the presentation of a post-hoc sub-group analysis from the TITAN study of the ITT results of patients that have previously been treated with ≤1 protease inhibitor (PI) was most representative of the extension to listing being sought. The Committee noted the results in this early treatment experienced patient (ETEP) group was not statistically significantly different at week 48 or week 96 for the primary outcome of proportion of patients with virological response < 400 copies per mL. With respect to virological response defined as viral load, the point estimate for the proportion of patients achieving a response remains higher with darunavir/ritonavir treatment that with lopinavir/ritonavir treatment until approximately week 48. For the secondary outcome, virological response < 50 copies per mL, the ITT results from TITAN show for the early treatment group show that darunavir/ ritonavir was not different to lopinavir/ritonavir at week 48, and week 96.

The number of virological failures (ITT) by week 96 was lower in the darunavir/ ritonavir population that in the lopinavir/ritonavir group (13.8% compared with 25.6%). Fewer virological failures treated with darunavir/ritonavir than with lopinavir/ritonavir lost susceptibility to other PIs. No separate data were available for the ETEP group.

The PBAC noted that the submission claimed that in the TITAN study "the only consistent and clinically meaningful difference at both week 48 and week 96 was diarrhoea" which favours darunavir. However, the Committee noted the data also showed significant differences in toxicity in favour of lopinavir for nervous systems disorders (at weeks 48 and 96) and overall skin and subcutaneous tissue disorders (at week 48 only).

The PBAC concluded that for effectiveness darunavir/ritonavir was non-inferior to lopinavir/ritonavir, and that, while the toxicity profiles were different, the overall impact in terms of cost of management would be similar.

There was uncertainty associated with the place of darunavir in the early treatment of HIV. Advice from expert clinicians confirmed that the clinical algorithm for early treatment HIV is rapidly evolving, and factors such as the availability of resistance testing, new drug classes, new formulations and pill burden would all impact treatment choice.

Recommendation:
DARUNAVIR, tablets, 150 and 300 mg (as ethanolate).

Amend the current restriction to read as follows:

Restriction:	Section 100 (Highly Specialised Drugs Program) Private hospital authority required Treatment, in combination with other antiretroviral agents, and co-administered with 100 mg ritonavir twice daily, 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, 1 antiretroviral regimen.
Pack size:	120 (300 mg), 240 (150 mg)

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 earlier access to darunavir for Australians living with HIV/AIDS.