PUBLIC SUMMARY DOCUMENT
Product: DARUNAVIR, tablet, 400 mg (as ethanolate), Prezista®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission requested a Section 100 (Highly Specialised Drugs Program) listing for the treatment in combination with other antiretroviral agents, and co-administered with 100 mg ritonavir once daily, of HIV infection in a protease inhibitor naïve 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.

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 new strength and the extended therapeutic indication of protease inhibitor-naïve HIV-1 patients had not previously been considered by the PBAC.

3. Registration Status

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

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

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug Program)
Private Hospital Authority Required
Treatment, in combination with other antiretroviral agents, and co-administered with 100 mg ritonavir once daily, of HIV infection in a protease inhibitor naïve 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.

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 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 three to six different antiretroviral therapies (e.g. nucleoside/nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors) and those which are restricted for use in salvage patients (e.g. tipranavir and enfuvirtide).

Inclusion of darunavir 400 mg on the PBS would allow earlier access to darunavir in a protease-inhibitor naïve patient who may be infected with PI-resistant HIV virus or who is unsuitable for other PIs.

6. Comparator

The submission nominated ritonavir boosted lopinavir (dosed at 800 mg/200 mg per day) as the comparator. The PBAC did not consider ritonavir boosted lopinavir to be the appropriate comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented one direct, multi-centre, open-label, randomised, controlled trial of ritonavir boosted darunavir (800/100 mg once daily) versus ritonavir boosted lopinavir (800/200 mg once daily) in treatment naïve patients with HIV infection (ARTEMIS).

The key trial was published at the time of submission as follows:

Trial ID/First author	Protocol title/Publication title	Publication citation
ARTEMIS 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.	AIDS 2008: 22(12); 1389-97
Mills A et al (2009)	Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-Week analysis.	AIDS (2009) 23:13; 1679-1688
Cohen C. (2009)	The ARTEMIS trial: Once-daily darunavir/ritonavir in the management of treatment-naive, HIV-infected patients.	T Future HIV Therapy (2009) 3:2; 121-133
Estrada V, Fuster M. (2008)	Darunavir in treatment-naïve patients. The ARTEMIS study.	Enfermedades Infecciosas y Microbiologia Clinica. 2008 Oct; 26 Suppl 10:10-3. Spanish

8. Results of Trials

The primary outcome of the ARTEMIS trial was virologic response, defined as a confirmed plasma viral load < 50 copies/mL at Week 48. The trial demonstrated non-inferiority of darunavir to lopinavir against its pre-specified minimal difference of 12% in viral load <50 copies/mL at 48 weeks.

At 96 weeks there was a significant difference favouring darunavir in percentage of patients achieving a viral load of <50 copies/mL, a secondary outcome of the ARTEMIS trial. There were no statistical differences in other secondary efficacy outcomes, supporting the non-inferiority of darunavir to lopinavir.

For PBAC's comments on these results, see Recommendation and Reasons.

The comparative toxicity of darunavir and lopinavir mostly favoured darunavir at 48 weeks but with no difference in adverse events at 96 weeks. Treatment with darunavir was

associated with significantly less episodes of diarrhoea. At both time points the rates of Grade 3 and 4 adverse events were comparable between the drugs with no occurrence of Grade 3 or 4 diarrhoea in either group ≥1%. No additional safety concerns were apparent for darunavir over lopinavir.

9. Clinical Claim

The submission described darunavir as superior to lopinavir in terms of efficacy, based upon the proportion of patients achieving a viral load <50 copies/mL and superior in terms of safety and tolerability.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis for ritonavir boosted darunavir as compared with ritonavir boosted lopinavir. The equi-effective doses were those administered in the ARTEMIS trial (800/100 mg darunavir/ritonavir once daily and 800/200 mg lopinavir/ritonavir once daily).

During the evaluation an additional analysis was conducted comparing the cost of ritonavir boosted atazanavir to ritonavir boosted darunavir.

The drug cost per patient per year estimated for ritonavir boosted darunavir (800/100 mg once daily), ritonavir boosted lopinavir (800/200 mg once daily), unboosted atazanavir (400 mg once daily) and ritonavir boosted atazanavir (300/100 mg once daily) were all less than $15,000.

Based on drug cost per patient per year, when ritonavir boosted darunavir was compared with unboosted atazanavir, ritonavir boosted darunavir was associated with cost savings to the PBS. Alternatively, when ritonavir boosted darunavir was compared with ritonavir boosted atazanavir there was a net cost to the PBS.

11. Estimated PBS Usage and Financial Implications

The net financial savings per year to the PBS were estimated by the submission to be less than $10 million per year in the fifth year of listing. The submission's estimate was uncertain as it was derived from its uncertain forecast of patient numbers. A recalculated indicative estimate undertaken during the evaluation which assumed an equal substitution of darunavir for lopinavir, unboosted atazanavir and boosted atazanavir and gave a net cost of less than $10 million per year to the PBS in the fifth year. The evaluation considered there was unlikely to be any use outside of the requested restriction.

12. Recommendation and Reasons

The PBAC agreed that the restriction wording suggested in the submission is appropriate.

The PBAC did not agree with the submission's nomination of ritonavir boosted lopinavir (dosed at 800/200 mg daily) as the appropriate comparator for ritonavir booster darunavir (dosed at 800/100 mg daily). Instead, the Committee considered ritonavir boosted atazanavir (dosed at 300/100 mg daily) is the more appropriate comparator for ritonavir boosted darunavir in treatment naïve and protease inhibitor naïve patients, although acknowledging that a proportion of the use of atazanavir in this patient group will be unboosted (dosed at 400

mg daily), so that using a weighted mix of boosted and unboosted atazanavir is the most appropriate approach.

The Committee considered atazanavir to be the more appropriate comparator because this is consistent with the most recent treatment guidelines which nominate ritonavir boosted atazanavir and ritonavir boosted darunavir as the preferred protease inhibitor (PI) based regimens for treatment-naïve patients, with ritonavir boosted lopinavir now listed as an alternative rather than preferred regimen, except in pregnant women.

Additionally, the analysis of the Australian HIV Observation Database (AHOD) data from 2006 onwards supports the use of atazanavir as the comparator. Using data from 2006 and later, atazanavir (not specified whether boosted or unboosted) accounts for 22 (40%), lopinavir accounts for 16 (29%), and other PIs for 17 (31%) of the PI treatments in treatment naïve patients. AHOD data also shows that the most commonly used PI for previously PI naïve patients after 1 January 2006 was atazanavir at 53.3% followed by boosted lopinavir at 35.6%.

The submission's assertion that a significant proportion of treatment naïve patients who received atazanavir are likely to have received atazanavir unboosted (which was based upon the TGA approved Product Information for atazanavir and the PBPA relativity sheets), was not considered justified by PBAC as the most recent US and Australian clinical guidelines recommend ritonavir boosted atazanavir for this group of patients. Additionally, the current PBS restriction for atazanavir does not restrict use to unboosted atazanavir for naïve patients and boosted atazanavir for treatment experienced patients. The Committee acknowledged that it will be difficult to establish the exact proportions of use of unboosted and boosted atazanavir in treatment naïve and PI naïve patients for any future submission, but that this should be justified using the best available evidence at the time.

The Committee noted the opinion of two clinical experts on the issue of the appropriate comparator. The PBAC indicated it would welcome the expert opinions of a wider sample of the Australasian Society for HIV Medicine (ASHM) membership, if appropriate, in any future submission.

The Committee noted that the submission presented evidence from one direct, multi-centre, open-label, randomised, controlled trial of ritonavir boosted darunavir versus ritonavir boosted lopinavir in treatment naïve patients with HIV infection (ARTEMIS). No evidence from a direct or indirect comparison of atazanavir (boosted or unboosted) with boosted darunavir was presented. Although acknowledging that at the time the ARTEMIS study design was developed, ritonavir boosted lopinavir was the appropriate comparative treatment, this is no longer the case. In the absence of data comparing the efficacy and safety of darunavir versus atazanavir in treatment naïve and PI naïve patients, the Committee was unable to form a view on the comparative effectiveness and cost of these two treatments.

The PBAC therefore rejected the submission because of the inappropriate choice of comparator and because there was no clinical- or cost-effectiveness data provided to allow a comparison against the appropriate comparator, atazanavir with or without ritonavir.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

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 is committed to ongoing interaction with the PBAC with a view to ensuring access to darunavir through the PBS for patients with HIV.