PUBLIC SUMMARY DOCUMENT
Product: Tenofovir disoproxil fumarate with emtricitabine and efavirenz, tablet, 300 mg – 200 mg – 600 mg, Atripla®
Sponsor: Gilead Sciences Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) private hospital authority required listing for tenofovir disoproxil fumarate, emtricitabine and efavirenz in a fixed dose combination for the treatment of HIV infected patients.

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 combination drug had not previously been considered by the PBAC.

3. Registration Status

Atripla was TGA registered on 3 August 2009 and is indicated for the treatment of HIV infected adults over the age of 18 years. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of tenofovir disoproxil fumarate, emtricitabine and efavirenz in treatment-naïve and treatment-experienced adults.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private hospital authority required
Treatment 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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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.

Typically, standard medical management of HIV infection consists of combinations of different antiretroviral therapies (e.g. nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)).

Fixed dose combination products such as Atripla may simplify regimens and improve medication adherence for HIV patients.

6. Comparator

The submission nominated concomitant use of the individual components, tenofovir disoproxil fumarate, emtricitabine and efavirenz, as the main comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented one randomised, cross-over pharmacokinetic trial evaluating the bioequivalence of Atripla with the individual drugs tenofovir disoproxil fumarate (300 mg), emtricitabine (200 mg) and efavirenz (600 mg) in healthy volunteers.

Publication details of the trial presented are in the following table.

Trial/First author	Protocol title/Publication title	Publication citation
Mathias AA et al (2007)	Bioequivalence of efavirenz / emtricitabine / tenofovir disoproxil fumarate single-tablet regimen.	J Acquir Immune Defic Syndr 2007; 46(2): 167-173

8. Results of Trials

The results of the pharmacokinetic comparison of Atripla and individual drugs are shown in the table below.

Parameter	Geometric LS Means		Geometric LS mean ratio (%)	90% CI
	Test (Atripla)	Reference (individual products)		
Tenofovir DF	**(N = 45)**	**(N = 45)**		
C_{max}(ng/mL)	307.25	335.93	91.46	84.64, 98.83
$AUC_{0\text{-}last}$ (ng•h/mL)	1,845.03	1,858.15	99.29	91.02, 108.32
AUC_{inf} (ng•h/mL)	2,218.24	2,208.41	100.45	93.22, 108.23
Emtricitabine	**(N = 45)**	**(N = 45)**		
C_{max}(ng/mL)	2,066.48	2,325.96	88.84	84.02, 93.94
$AUC_{0\text{-}last}$ (ng•h/mL)	10,523.83	10,740.78	97.98	94.90, 101.16
AUC_{inf} (ng•h/mL)	10,694.43	10,916.98	97.96	94.86, 101.16
Efavirenz	**(N = 44)**	**(N = 44)**		
C_{max}(ng/mL)	2,190.20	2,192.55	99.89	93.37, 106.88
$AUC_{0\text{-}last}$ (ng•h/mL)	120,841.0	126,231.3	95.73	90.50, 101.26
AUC_{inf} (ng•h/mL)	137,106.6	144,030.3	95.19	88.92, 101.91

AUC = area under the curve; C_{max} = maximal plasma concentration; DF = disoproxil fumarate; LS = least squares; mL = millilitre; ng = nanogram

The PBAC noted that the pharmacokinetic results indicated that Atripla versus its individual drugs are within the pre-specified non-inferiority margin of 80 % to 125% and can be considered bioequivalent in healthy subjects without HIV infection.

The PBAC noted similar levels of adverse events occurred in healthy volunteers given Atripla versus its individual component drugs. An extended assessment of comparative harm did not reveal any additional safety concerns for Atripla compared with the recognised safety concerns associated with the individual drugs.

9. Clinical Claim

The submission described Atripla as having similar effectiveness and toxicity compared to concomitant tenofovir disoproxil fumarate and emtricitabine and efavirenz. This was considered reasonable by the PBAC.

10. Economic Analysis

The submission presented a cost-minimisation analysis.

11. Estimated PBS Usage and Financial Implications

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

12. Recommendation and Reasons

The PBAC recommended listing of tenofovir disoproxil fumarate with emtricitabine and efavirenz (Atripla®) as Section 100 Highly Specialised Drugs (HSD) Program for the treatment of HIV infection on a cost-minimisation basis compared with the corresponding strengths of the individual components given concomitantly. The PBAC noted that the product meets the requirements of the Guidelines for the listing of fixed combination products.

The PBAC accepted that the individual components of the Atripla were the appropriate comparators. The PBAC noted that although the submission did not present clinical evidence of health related outcomes, a randomised, cross-over pharmacokinetic trial was presented, which demonstrated the bioequivalence of Atripla with the individual components tenofovir DF (300 mg) and emtricitabine (200 mg) and efavirenz (600 mg) in healthy volunteers which the PBAC considered appropriate. The pharmacokinetic results indicated that Atripla versus its individual drugs are within the pre-specified non-inferiority margin of 80 % to 125% and can be considered bioequivalent in healthy subjects without HIV infection. The PBAC noted that similar levels of adverse events were observed for both Atripla and its individual components drugs and that there were no additional safety concerns for Atripla compared with the recognised safety concerns associated with the individual drugs.

Recommendation:

TENOFOVIR DISOPROXIL FUMARATE with EMTRICITABINE and EFAVIRENZ, tablet, 300 mg-200 mg-600 mg

Restriction:	Section 100 (Highly Specialised Drugs Program) Private hospital authority required Treatment 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:	30

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

Gilead Sciences welcomes the PBAC recommendation for Section 100 listing of ATRIPLA for the treatment of eligible HIV infected patients.