PUBLIC SUMMARY DOCUMENT
Product: Tenofovir with emtricitabine and rilpivirine, tablet containing tenofovir disoproxil fumarate 300 mg with emtricitabine 200 mg and rilpivirine hydrochloride 25 mg, Eviplera®
Sponsor: Gilead Sciences Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission requested a S100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in a patient with a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease.

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

The fixed combination drug had not previously been considered by the PBAC.

3. Registration Status

Tenofovir with emtricitabine and rilpivirine, Eviplera®, was registered by the TGA on 23 January 2012 for the following indication:

- Treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA ≤ 100,000 copies per mL at the start of therapy.

4. Listing Requested and PBAC's View

Section 100 listing
Public Hospital Authority Required (STREAMLINED)
Private Hospital Authority Required
Initial treatment of HIV infection in combination with other antiretroviral agents in a patient with a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease;
Continuing treatment of HIV infection in combination with other antiretroviral agents where the patient has previously received PBS-subsidised therapy of HIV infection.

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. In the absence of effective antiretroviral treatment, HIV infection leads to severe immune deficiency and the development of the systemic opportunistic infections and cancers that define the onset of the final stage of HIV infection, the acquired immune deficiency syndrome (AIDS), and ultimately results in death.

Typically, standard medical management of HIV-1 infection consists of combinations of different antiretroviral therapies (e.g. nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)).

The submission proposed that the place in therapy of tenofovir with emtricitabine and rilpivirine is to provide an alternative combination tablet for the treatment of HIV.

6. Comparator

The submission nominated the fixed dose combination product tenofovir disoproxil fumarate (DF) (300 mg) with emtricitabine (200 mg) and efavirenz (600 mg), Atripla® as the comparator. This was accepted by the PBAC.

7. Clinical Trials

The basis of the submission was two direct randomised comparative trials, ECHO and THRIVE, comparing rilpivirine (25 mg) plus two N(t)RTIs and efavirenz (600 mg) plus two N(t)RTIs in treatment naïve HIV patients. Subjects enrolled in both the ECHO and THRIVE trials were treatment naïve only. The THRIVE trial included some patients who did not receive all three compounds in Eviplera or Atripla, i.e. they received different N(t)RTIs.

The ECHO and THRIVE trials were both 96 weeks in duration, with the primary outcome reported at 48 weeks. The primary outcome for both the ECHO and THRIVE trials was the proportion of patients with plasma viral load less than 50 HIV-1 RNA copies/mL at week 48. In order to qualify as a virologic responder, using the time to loss of virologic response (TLOVR) algorithm, a subject must have had two consecutive values below the specified threshold. For loss of response, two consecutive values above the threshold were required. The threshold specified for the primary efficacy outcome in both trials was 50 copies/mL. Both the ECHO and THRIVE trials used a maximum allowable difference of 12% according to the TLOVR algorithm as defined by the FDA.

Details of the studies published at the time of submission are shown in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
ECHO Molina J et al 2011	Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naïve adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial.	The Lancet. 2011 Jul; 378:238-46.
THRIVE Cohen C et al 2011	Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial.	The Lancet. 2011 Jul; 378:229-37.
Pozniak AL et al 2010	Efficacy and safety of TMC278 in antiretroviral-naïve HIV-1 patients: Week 96 results of a phase IIb randomized trial	AIDS 2010; 24(1): 55-65.
Wilkin A et al 2010	TMC278 shows favourable tolerability and non-inferior efficacy compared to efavirenz over 192 weeks in HIV-1-infected treatment-naïve patients	Infection 2010; 38: S63-64.

8. Results of Trials

Efficacy Trials

The results for the primary outcome of the ECHO and THRIVE trials, proportion of virological responders, defined as a viral load less than 50 copies/mL at week 48 showed both rilpivirine and efavirenz (plus tenofovir DF with emtricitabine or plus two N(t)RTIs) resulted in high virologic response rates (84.3% vs. 81.5%, meta-analysis). As the lower limit of the 95% confidence interval was above -12% in both the ECHO and THRIVE trials, the non-inferiority criteria were met ($p<0.0001$).

Although not presented in the submission, it is evident that statistically significantly more patients treated with two N(t)RTIs plus rilpivirine, compared to efavirenz, had treatment failure due to virologic failure (risk difference 4.2%, 95% CI: 1.5, 6.9). Statistically significantly more patients treated with two N(t)RTIs plus efavirenz, compared to rilpivirine, discontinued treatment due to adverse events (risk difference 4.7%, 95% CI: 6.9, 2.5). As patients in THRIVE were allowed N(t)RTIs other than tenofovir DF / emtricitabine treatment, the results from ECHO may be more relevant.

Across both ECHO and THRIVE trials, patients in the rilpivirine plus two N(t)RTIs treatment groups had greater resistance to lamivudine, abacavir and emtricitabine. Alternatively, patients in the efavirenz plus two N(t)RTIs treatment groups had greater resistance to zidovudine.

The cross-resistance to other NNRTIs and N(t)RTIs may have an impact on the choice of NNRTI for first-line treatment.

Bio Equivalence Trial

The submission presented the results of pharmacokinetic parameters for fixed dose versus free dose tenofovir DF/emtricitabine/rilpivirine from Study 103.

For PBAC's view of these results, see Recommendation and Reasons.

A summary of the adverse events reported in the clinical trials showed there was no statistically significant difference in the incidence of adverse events (all grades) between rilpivirine plus two N(t)RTIs and efavirenz plus two N(t)RTIs (ECHO - RR 0.95, 95% CI:0.90, 1.00; THRIVE - RR 1.00, 95%CI 0.95, 1.05). In addition, there was no statistically significant difference in the incidence of any serious adverse events between rilpivirine plus two N(t)RTIs and efavirenz plus two N(t)RTIs (ECHO - RR 0.74, 95% CI:0.44, 1.24; THRIVE - RR 0.91, 95%CI 0.52, 1.59).

However, the rate of treatment-related adverse events was lower in subjects treated with rilpivirine plus two N(t)RTIs (42.5% in ECHO and 50.3% in THRIVE) than in subjects treated with efavirenz plus two N(t)RTIs (62.2% in ECHO and 66.0% in THRIVE). Rilpivirine plus two N(t)RTIs was statistically significantly associated with fewer adverse events leading to discontinuation and fewer skin and neurologic adverse events than efavirenz plus two N(t)RTIs across both the ECHO and THRIVE trials.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. The submission stated that the safety profile of Eviplera is likely to be

consistent with the safety profile of its component products and that in general, treatment with two N(t)RTIs + rilpivirine was safe and well-tolerated.

9. Clinical Claim

The submission described Eviplera as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over Atripla.

Based on the supporting data, the PBAC accepted the submission's claim that Eviplera is non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over Atripla, with the caveat that treatment with rilpivirine plus two N(t)RTIs is associated with more virological failure and cross-resistance to other NNRTIs and N(t)RTIs than efavirenz plus two N(t)RTIs.

10. Economic Analysis

The submission presented a cost-minimisation analysis.

Both the ECHO and THRIVE trials relied upon doses of 25 mg for rilpivirine and 600 mg for efavirenz. In addition, the submission presented evidence from an international Phase 2b randomised dose-finding study of rilpivirine in treatment-naïve HIV-1 infected patients (Pozniak et al., 2010). Within this study, the lowest assessed dose of rilpivirine (25 mg/day) demonstrated sustained efficacy comparable with 600 mg of efavirenz and was selected for further clinical development.

Based on this evidence, the PBAC considered that it is reasonable to assume that 25 mg/day rilpivirine and 600 mg/day efavirenz are equi-effective.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated/year was estimated by the submission to be less than 10,000 in Year 5. The estimate was uncertain.

The net financial cost to the PBS was estimated by the submission to be between $10 and $30 million in Year 5. The estimate was uncertain given the imprecision in the estimated number of patients treated.

The net cost to the PBS in 2015 is estimated at less than $10 million where Eviplera is listed for treatment-naïve only patients compared to an increased net cost though in the same range if listed for all HIV-1 patients.

12. Recommendation and Reasons

The PBAC recommended listing of tenofovir disoproxil fumarate with emtricitabine and rilpivirine hydrochloride (Eviplera®) in the Section 100 Highly Specialised Drugs (HSD) Program for the treatment of human immunodeficiency virus (HIV) infection on a cost-minimisation basis compared with the Atripla® (tenofovir disoproxil fumarate with emtricitabine and efavirenz). The doses of tenofovir DF and emtricitabine included in Eviplera are identical to the doses of tenofovir DF and emtricitabine. The PBAC considered the therapeutic relativity of Eviplera and Atripla depended on the equi-effective doses of ripilvirine and efavirenz. The PBAC considered the equi-effective doses to be 25 mg/day

rilpivirine and 600 mg/day efavirenz. The PBAC noted that the product meets the requirements of the Guidelines for the listing of fixed combination products.

The PBAC noted that the TGA Delegate's Summary had been received just prior to the PBAC meeting and that the Delegate proposed to approve Eviplera for registration for the treatment of HIV-1 infection in anti-retroviral treatment-naïve adult patients. Therefore, the PBAC considered that that there was some uncertainty surrounding the place of Eviplera therapy in practice as the data presented were from treatment naïve patients only, but the requested restriction did not prevent patients using Eviplera as a second line treatment. However, the PBAC was confident that prescribers treating patients with HIV had the necessary expertise that would ensure the appropriate use of Eviplera. Therefore, the PBAC considered that a restriction wording consistent with that of the comparator Atripla (tenofovir with emtricitabine and efavirenz) was appropriate.

However, the PBAC recommended amending the current restriction for both the triple combination therapies, Eviplera and Atripla®, as highlighted by strikethrough above, for clarity. The PBAC considered that triple therapy was unlikely to be used in combination with other anti-retrovirals and therefore the wording "in combination with other antiretroviral agents" was redundant. It may cause confusion as doctors may think they need to prescribe another agent as well as the triple therapy agent to be eligible for PBS-subsidised treatment. This is also consistent with the proposed TGA Delegate's wording. The PBAC also requested the Secretariat seek advice from the Australasian Society for HIV Medicine (ASHM) on the appropriateness of this wording.

The PBAC accepted the fixed dose combination product tenofovir disoproxil fumarate (DF) 300 mg with emtricitabine (200 mg) and efavirenz (600 mg) (Atripla®) is the appropriate comparator.

The submission presented a Phase 1, randomised, crossover bioequivalence trial (Study 103), and the PBAC considered that the pharmacokinetic results demonstrated that Eviplera versus its individual components are within the pre-specified non-inferiority margin. Therefore, bioequivalence can be accepted in healthy subjects without HIV infection.

For comparative efficacy, the submission presented two direct randomised comparative trials, ECHO and THRIVE, comparing rilpivirine (25 mg) plus two non-nucleoside/tide reverse transcriptase inhibitors (N(t)RTIs) and efavirenz (600 mg) plus two N(t)RTIs in treatment naïve HIV patients. ECHO and THRIVE were both of 96 weeks duration of treatment naïve patients only.

For the primary outcome of virologic response (plasma viral load < 50 HIV-1 RNA copies/mL) at 48 weeks both rilpivirine and efavirenz (plus tenofovir DF with emtricitabine or plus two N(t)RTIs) resulted in high virologic response rates (84.3% vs. 81.5%, meta-analysis). As the lower limit of the 95% confidence interval was above -12% in both the ECHO and THRIVE trials, the non-inferiority criteria were met ($p<0.0001$).

With regard to cross resistance, the PBAC noted of the patients with virologic failure who were treated with rilpivirine plus two N(t)RTIs in the ECHO and THRIVE trials 51.3% and 47.6% were resistant to efavirenz. However, no patients with virologic failure who were treated with efavirenz plus two N(t)RTIs were resistant to rilpivirine.

Based on the supporting data, the PBAC accepted the submission's claim that Eviplera is non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over Atripla, with the caveat that rilpivirine plus two N(t)RTIs is associated with more virological failure and cross-resistance to other NNRTIs and N(t)RTIs than efavirenz plus two N(t)RTIs.

The PBAC noted the advice of the Highly Specialised Drugs Working Party which supported listing tenofovir with emtricitabine and rilpivirine as a HSD under Section 100.

Recommendation:
TENOFOVIR DISOPROXIL FUMARATE with EMTRICITABINE and RILPIVIRINE HYDROCHLORIDE, tablet, 300 mg-200 mg-25 mg

Restriction:	Section 100 listing Public Hospital Authority Required (STREAMLINED) Private Hospital Authority Required Initial treatment of HIV infection ~~in combination with other antiretroviral agents~~ in a patient with a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease; Continuing treatment of HIV infection ~~in combination with other antiretroviral agents~~ where the patient has previously received PBS-subsidised therapy of HIV infection.
Maximum qty:	60
Rpt:	5

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 to list Eviplera (tenofovir DF/emtricitabine/rilpivirine hydrochloride) on the PBS for the treatment of patients with HIV infection.