PUBLIC SUMMARY DOCUMENT
Product: Cobicistat+elvitegravir+emtricitabine+tenofovir, tablet, cobicistat 150 mg, elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, Stribild®
Sponsor: Gilead Sciences Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested Section 100 Highly Specialised Drugs Program Private Hospital Authority Required and Public Hospital Authority required (STREAMLINED) listings for treatment of HIV infection 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

This product had not been considered previously by the PBAC.

3. Registration Status

Stribild was registered by the TGA on 22 February 2013 as follows:

- Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults. Stribild is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

4. Listing Requested and PBAC's View

Section 100 Highly Specialised Drugs
Authority required (STREAMLINED)
Initial treatment of HIV infection in a patient with a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease.

Authority required (STREAMLINED)
Continuing treatment of HIV infection where the patient has previously received PBS-subsidised therapy for HIV infection.

For PBAC's view, see Recommendation & Reasons.

5. Clinical Place for the Proposed Therapy

Human immunodeficiency virus (HIV) infection is a chronic, immunosuppressive infection. As the disease progresses, HIV infection leads to severe immune deficiency and/or the development of the opportunistic infections and cancers that define the acquired immune deficiency syndrome (AIDS).

Standard medical management of HIV-1 infection consists of combinations of different antiretroviral therapies.

The submission proposed Stribild as an alternative treatment option in both treatment-naïve and treatment-experienced HIV patients, who have a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease.

For PBAC's view, see Recommendation & Reasons.

6. Comparator

The main comparator nominated by the submission was the individual component products given concurrently. Secondary comparisons of Stribild versus Atripla (fixed dose combination of tenofovir/emtricitabine/efavirenz) and tenofovir/emtricitabine/atazanavir/ritonavir were also presented.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented two bioequivalence studies (GS-0101, GS-0110), comparing Stribild to separate administration of its individual components. The submission also presented direct comparisons of Stribild vs. Atripla (GS-0102) and Stribild vs. tenofovir/emtricitabine/atazanavir/ritonavir (GS-0103) in treatment-naïve HIV-1 patients.

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

Trial ID/ First author	Protocol title/ Publication title	Publication citation
GS-0101 German et al (2010)	Pharmacokinetics and bioavailability of an integrase and novel pharmacoenhancer-containing single-tablet fixed-dose combination regimen for the treatment of HIV.	Journal of Acquired Immune Deficiency Syndromes 55: 323-329
GS-0102 Sax et al (2012)	Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: A randomised, double-blind, phase 3 trial, analysis of results after 48 weeks.	Lancet 379: 2439-2448
GS-0103 DeJesus et al (2012)	Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: A randomised, double-blind, phase 3, non-inferiority trial	Lancet 379: 2429-2438

8. Results of Trials

Neither of the included bioequivalence studies directly compared Stribild to its individual components administered concurrently and the results from these studies indicated that the fixed dose combinations did not meet the pre-specified bioequivalence margins against individual components.

The submission presented the proportion of patients with virological success (HIV-1 RNA < 50 copies/mL) at 48 weeks, using the FDA-defined snapshot algorithm (defines a responder

at pre-defined time points within an allowed period of four days), as the primary outcome for both of the clinical trials (GS-0102 and GS-0103).

The purpose of the primary efficacy analyses was to assess non-inferiority of Stribild against other first-line therapies. Non-inferiority was concluded when the lower bound of the two-sided 95% confidence interval for difference of response rate (Stribild − comparator) was greater than -12%.

Virological response (HIV-1 RNA <50 copies/mL) at Week 48 using snapshot analysis in a modified intention-to-treat population

Trial (comparator)	**Stribild** n/N (%)	**Comparator** n/N (%)	**% Difference (95% CI) Stribild - comparator Stratum weighted**	**% Difference (95% CI) Stribild – comparator Unweighted (post-hoc)**	**NNT (95% CI)**
GS-0102 (Atripla)	305/348 (87.6)	296/352 (84.1)	3.6 (-1.6, 8.8)	3.6 (-1.6, 8.7)	29 (12, -62)
GS-0103 (TDF/FTC/ATV/RTV)	316/353 (89.5)	308/355 (86.8)	3.0 (-1.9, 7.8)	2.8 (-2.0, 7.5)	37 (14, -50)

Abbreviations: ATV, atazanavir; CI, confidence interval; FTC, emtricitabine; NNT, number needed to treat; RTV, ritonavir; TDF, tenofovir

The primary efficacy analyses indicated that Stribild is non-inferior to both Atripla and tenofovir/emtricitabine/atazanavir/ritonavir in terms of virological response at week 48 in treatment-naïve HIV-1 patients as the pre-specified non-inferiority margin of 12% was met.

In terms of safety, Stribild was associated with higher rates of adverse events (13/43 subjects) and discontinuations (5/43 subjects) compared to tenofovir/emtricitabine (adverse events: 9/43 subjects; discontinuations: 0/43 subjects) but had similar rates to ritonavir-boosted elvitegravir. Adverse event profiles were similar for both the preliminary test formulation and the final marketed formulation.

Specifically the PBAC noted that in comparison with Atripla, Stribild was associated with a higher rate of:

- Serious adverse events – 41 out of 348 patients on Stribild (11.8%) vs. 24 out of 352 patients on Atripla (6.8%). This included patients who suffered an infection or infestation (20 events (5.7%) vs. 6 (1.7%))
- Creatinine abnormalities – 29 events (8.4%) vs. 4 (1.1%)
- Proteinuria – 144 (41.5%) vs. 101 (28.8%)

The PBAC noted also that the USA's Food and Drug Administration (FDA) has made note of the higher incidence of renal-related adverse events with Stribild. The PBAC noted also the sponsor's commitment to the continued monitoring of the risk of renal adverse events as part of its ongoing post-marketing agreements.

The PBAC noted a lower incidence of the following adverse events in patients taking Stribild compared with patients taking Atripla:

- Neurological and psychiatric events – 149 (42.8%) vs. 220 (62.5%)
- Rash events – 59 (17%) vs. 98 (27.8%)

The PBAC considered that the trial population was not entirely consistent with the requested PBS population, in that patients enrolled in the trials were naïve to antiretroviral therapy. Overall, however, the PBAC considered that the safety of Stribild in a treatment-experienced population was likely comparable with that in a treatment-naïve population, and concluded that Stribild is non-inferior to Atripla for comparative safety. The differential safety profile of Stribild compared with Atripla was considered to provide an alternative therapeutic option for patients unable to tolerate Atripla.

No data in treatment-experienced patients was presented in the submission.

For PBAC's view, see Recommendation & Reasons.

9. Clinical Claim

The submission described Stribild as bioequivalent to its individual components.

The submission claimed Stribild was non-inferior in terms of efficacy, and comparable in terms of safety to Atripla and tenofovir/emtricitabine/atazanavir/ritonavir in treatment-naïve patients.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis of Stribild compared to its individual components. Equi-effective doses were based on the claim that Stribild is bioequivalent to the corresponding strengths of the individual components administered concurrently.

For PBAC's view, see Recommendation & Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patient numbers to be less than 10,000 per year at an estimated net cost to the PBS of less than $10 million in Year 5 of listing.

The PBAC considered the submission's estimates of PBS usage and financial implications to be uncertain.

12. Recommendation and Reasons

The PBAC recommended the listing of Stribild on the PBS, on a cost-minimisation basis with Atripla. The PBAC also recommended that a cost-offset be applied to account for increased renal monitoring required in patients using Stribild compared with those using Atripla.

The PBAC did not accept the economic analysis, which was based on the components being administered concurrently (excepting cobicistat, which was included at no extra cost), was appropriate in view of the lack of conclusive non-inferiority with the components and that, in practice, the true comparator would be Atripla.

The PBAC considered that Atripla was the most appropriate comparator, rather than the individual components given concurrently, as Atripla would be the most likely therapy replaced in clinical practice.

The PBAC agreed that Stribild was non-inferior to Atripla and tenofovir/emtricitabine/atazanavir/ritonavir in treatment naïve patients. The PBAC considered that the comparative effectiveness and safety of Stribild may be reasonably extrapolated to a treatment-experienced population.

The PBAC recommended that the restriction for Stribild be consistent with that of Atripla, and that it therefore include both treatment-experienced and treatment-naïve patients.

The PBAC considered the submission's utilisation estimates to be highly uncertain and that the net overall cost to the PBS would be largely attributed to the higher price of Stribild compared with Atripla. The PBAC further considered that by pricing Stribild at a level equivalent to Atripla in treatment-naïve patients (rather than the component drugs of Stribild, as proposed in the submission), the risk of increased net cost to the PBS without additional incremental benefit over Atripla was mitigated. The PBAC also considered that the reduction in price would appropriately address the uncertainty in the submission's utilisation estimates.

The PBAC noted that currently, the *National Health (Highly Specialised Drugs program for hospitals) Special Arrangement 2010* includes only 'eligible medical practitioners' as authorised prescribers able to write prescriptions for supply of medicines under the Highly Specialised Drugs Program. Stribild is therefore out of scope for prescribing by nurse practitioners.

Recommendation:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
Cobicistat + elvitegravir + emtricitabine + tenofovir, Tablet, cobicistat 150 mg + elvitegravir 150 mg + emtricitabine 200 mg + tenofovir 300 mg	60	5	Stribild®	Gilead Sciences

Condition/Indication:	HIV infection
Treatment phase:	Initial treatment
Restriction:	Section 100 Highly Specialised Drugs Program Private Hospital Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have a CD4 count of less than 500 per cubic millimetre; OR Patient must have symptomatic HIV disease

Condition/Indication:	HIV infection
Treatment phase:	Continuing treatment

Restriction:	Section 100 Highly Specialised Drugs Program Private Hospital Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection.

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 welcomes the PBAC recommendation to list Stribild on the PBS.
However the sponsor disagrees with the recommendation to list Stribild on a cost minimisation basis with Atripla and also disagrees that there will be additional costs incurred for renal monitoring of Stribild. The sponsor will address these issues with the PBAC in a subsequent PBAC submission.