

## 5.05 ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE, FIXED-DOSE COMBINATION TABLET, 150 MG/ 150 MG/200 MG/10 MG, GENVOYA®, GILEAD SCIENCES

### 1 Purpose of Application

- 1.1 Section 100 Highly Specialised Drug Program: Authority Required (Streamlined) listing for elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (EVG/c/FTC/tenofovir alafenamide) fixed-dose combination (FDC) product for treatment of human immunodeficiency virus (HIV) infection in treatment-naïve patients and treatment-experienced patients.

### 2 Requested listing

- 2.1 The proposed PBS listing for EVG/c/FTC/tenofovir alafenamide was for initial treatment of HIV infection in treatment-naïve patients and for continuing treatment of HIV infection in treatment-experienced patients with a clinical indication to switch components of therapy (e.g. the occurrence of adverse effects or loss of viral suppression).

Name, Restriction, Manner of administration and Form	Max Qty	No. of Rpts	DPMQ	Proprietary Name and Manufacturer	
ELVITEGRAVIR + COBICISTAT + EMTRICITABINE + TENOFOVIR ALAFENAMIDE Tablet; 150 mg/150 mg/200 mg/10 mg	60	5	Public hospital: \$ [REDACTED] Community Access/ Private hospital: \$ [REDACTED]	TBC	Gilead Sciences
Treatment phase:	• Initial treatment				
Restriction:	• Section 100 HSD: Authority Required (Streamlined)				
Clinical criteria:	• Patient must be antiretroviral treatment naïve				
Treatment phase:	• Continuing treatment				
Restriction:	• Section 100 HSD: Authority Required (Streamlined)				
Clinical criteria:	• Patient must have previously received PBS-subsidised therapy for HIV infection				

DPMQ = dispensed price for maximum quantity; HSD = Highly Specialised Drug; TBC = to be confirmed

- 2.2 The submission provided a cost-minimisation analysis of EVG/c/FTC/tenofovir alafenamide versus the nominated comparator, elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (EVG/c/FTC/tenofovir DF).

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### 3 Background

- 3.1 TGA status at time of PBAC consideration: Not registered. The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, a positive TGA Delegate summary was available. The proposed TGA indication was:

- For the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older without any known mutation associated with resistance to the individual components.
- 3.2 EVG/c/FTC/tenofovir alafenamide had not been considered by the PBAC previously.
- 3.3 EVG/c/FTC/tenofovir DF (Stribild<sup>®</sup>) was originally considered by the PBAC in March 2013 and the PBAC recommended that a cost-offset be applied to EVG/c/FTC/tenofovir DF to account for increased renal monitoring compared to those patients using efavirenz/FTC/tenofovir DF (Atripla<sup>®</sup>). In November 2013, the PBAC accepted that EVG/c/FTC/tenofovir DF was non-inferior in terms of safety compared with efavirenz/FTC/tenofovir DF, and EVG/c/FTC/tenofovir DF was listed on the PBS with no cost-offsets in May 2014.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

#### **4 Clinical place for the proposed therapy**

- 4.1 The proposed drug is a FDC product containing four antiretrovirals for the treatment of HIV infection: elvitegravir, a HIV integrase strand transfer inhibitor (INSTI); cobicistat, an enhancer of CYP3A substrates; and emtricitabine and tenofovir alafenamide, which are nucleoside reverse transcriptase inhibitors (NRTIs).
- 4.2 It was proposed that EVG/c/FTC/tenofovir alafenamide would be used first line in treatment-naïve patients. In treatment-experienced virologically suppressed patients, the choice of therapy would be guided by the resistance profile, and EVG/c/FTC/tenofovir alafenamide would be used when appropriate. The ESC noted that the most recent US Department of Health and Human Services HIV treatment guidelines (Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, US Department of Health and Human Services) and the Australian commentary (Australian Commentary to the US Department of Health and Human Services Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescent) recommend EVG/c/FTC/tenofovir DF (Stribild<sup>®</sup>) as one option for first line therapy in treatment naïve patients. The ESC noted tenofovir alafenamide-containing regimens are not yet included in the guidelines. The ESC considered it may be appropriate to consider that the likely place in therapy for EVG/c/FTC/tenofovir alafenamide would be as first line.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

#### **5 Comparator**

- 5.1 The submission nominated elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (EVG/c/FTC/tenofovir DF) FDC (Stribild<sup>®</sup>) as the comparator.
- 5.2 This was the appropriate comparator for adult patients without renal impairment. For adolescents and patients with renal impairment, dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) FDC (Triumeq<sup>®</sup>) might be the more appropriate comparator, as EVG/c/FTC/tenofovir DF is not indicated for adolescents (12-18 years) and patients

with an estimated glomerular filtration rate below 70 mL/minute (Australian product information). The ESC agreed that Stribild is the main comparator, but that EVG/c/FTC/tenofovir alafenamide might also displace other TDF/FTC-containing single tablet and multi-tablet highly active antiretroviral therapies as well as DTG/ABC/3TC.

For more detail on PBAC's view, see section 7 "PBAC outcome".

## **6 Consideration of the evidence**

### **Sponsor hearing**

6.1 There was no hearing for this item.

### **Consumer comments**

6.2 The PBAC noted that no consumer comments were received for this item.

### **Clinical trials**

6.3 The submission was based on two head-to-head randomised controlled trials comparing EVG/c/FTC/tenofovir alafenamide to EVG/c/FTC/tenofovir DF in treatment-naïve patients (Study 104, n = 872; and Study 111, n = 872). These studies assessed efficacy and safety, and used a  $\pm 12\%$  margin for non-inferior efficacy to compare the agents. A randomised open-label trial comparing EVG/c/FTC/tenofovir alafenamide to pre-existing therapy (FTC/tenofovir DF plus third agent) in treatment-experienced patients (Study 109, n = 1,443) was also presented to support the claim that virologically suppressed patients on a tenofovir DF-containing regimen could switch to EVG/c/FTC/tenofovir alafenamide without loss of clinical efficacy. The ESC considered that because only a proportion of participants in the comparator arm of Study 109 received EVG/c-based plus TDF/FTC, and because the outcome for this group was not reported separately, the study did not allow for a direct comparison of EVG/c/FTC/tenofovir alafenamide versus EVG/c/FTC/TDF in treatment experienced patients.

6.4 Details of the trials presented in the submission are provided in the table below.

**Table 1: Trials presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
Study 104	A Phase 3, randomised, double-blind, study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment naïve adults.  Sax PE, Whol D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials.	6 October 2014  Lancet. 2015 385(9987):2,606-2,615
Study 111	A Phase 3, randomised, double-blind, study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment naïve adults.  Sax PE, Whol D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials.	13 October 2014  Lancet. 2015 385(9987):2,606-2,615
Study 109	A Phase 3 open-label safety study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects.	1 October 2014

Source: Table B-3, p30 of the submission

HIV = human immunodeficiency virus; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

6.5 The key features of the direct randomised trials are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome
<b>Treatment naïve</b>					
Study 104	872	R, DB, MC 48 weeks	Low	Treatment naïve; HIV-1 positive	HIV RNA < 50 copies/mL
Study 111	872	R, DB, MC 48 weeks	Low	Treatment naïve; HIV-1 positive	HIV RNA < 50 copies/mL
<b>Treatment experienced</b>					
Study 109	1,443	R, OL, MC 48 weeks	Moderate	Virologically suppressed; HIV-1 positive	HIV RNA < 50 copies/mL

Source: compiled during the evaluation

DB = double blind; HIV = human immunodeficiency virus; MC = multi-centre; OL = open label; R = randomised; RNA = ribonucleic acid

6.6 The ESC considered the risk of bias in the evidence reported for the safety endpoints from Study 109 to be moderate as it was an open-label study.

### Comparative effectiveness

6.7 The clinically relevant outcome for benefits was the proportion of patients with HIV ribonucleic acid (RNA) < 50 copies/mL, using the US Food and Drug Administration snapshot algorithm. This was the primary outcome in the three pivotal trials. This was the appropriate outcome measure.

6.8 **Table 3: Results for the proportion of patients with HIV RNA < 50 copies/mL across the direct randomised trials (full analysis sets)**

Treatment naïve	EVG/c/FTC/TAF, n/N (%)	EVG/c/FTC/TDF, n/N (%)	Difference in % (95% CI)
Study 104	405/435 (93.1%)	399/432 (92.4%)	1.0% (-2.6, 4.5)
Study 111	395/431 (91.6%)	385/435 (88.5%)	3.1% (-1.0, 7.1)
<b>Pooled analysis</b>	800/866 (92.4%)	784/867 (90.4%)	2.0% (-0.7, 4.7)
Treatment experienced	EVG/c/FTC/TAF, n/N (%)	FTC/TDF + 3 <sup>rd</sup> agent <sup>a</sup> , n/N (%)	Difference in % (95% CI)
Study 109	764/799 (95.6%)	369/397 (92.9%)	2.7% (-0.3, 5.6)

Source: Table B-17, p51; Table B-38, p75 of the submission; and Table 9-1, p96 of Study 109 CSR

c = cobicistat; CI = confidence interval; EVG = elvitegravir; FTC = emtricitabine; HIV = human immunodeficiency virus; RNA = ribonucleic acid; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

<sup>a</sup> Third agents: cobicistat + elvitegravir (~32%), efavirenz (~26%), ritonavir-boosted atazanavir (~15%), or cobicistat-boosted atazanavir (~27%)

6.9 In the analyses, virologic success was achieved in approximately 90% of patients, regardless of treatment, and the differences in percentages between treatment arms were not significant. EVG/c/FTC/tenofovir alafenamide was considered non-inferior to EVG/c/FTC/tenofovir DF in treatment-naïve patients and non-inferior to FTC/tenofovir DF plus third agent regimens in treatment-experienced patients as the lower bounds of the two-sided 95% confidence intervals (CI) were greater than the pre-specified -12% margin. This was appropriate.

**Comparative harms**

6.10 There were similar rates of adverse events and serious adverse events in treatment-naïve patients (Studies 104 and 111). The rates of discontinuation were also very similar. Rates of adverse events and serious adverse events were lower in treatment-experienced patients (Study 109).

**Table 4: Overview of the adverse events experienced (safety analysis sets)**

	Treatment naïve				Treatment experienced	
	Study 104		Study 111		Study 109	
	EVG/c/FTC/TAF	EVG/c/FTC/TDF	EVG/c/FTC/TAF	EVG/c/FTC/TDF	EVG/c/FTC/TAF	FTC/TDF + 3 <sup>rd</sup> agent <sup>a</sup>
N	435	432	431	435	959	477
Any AE	396 (91.0%)	392 (90.7%)	382 (88.6%)	390 (89.7%)	764 (79.7%)	368 (77.1%)
Grade 3 or 4 AE	36 (8.3%)	26 (6.0%)	35 (8.1%)	49 (11.3%)	61 (6.4%)	32 (6.7%)
Tx-related AE	182 (41.8%)	196 (45.4%)	160 (37.1%)	168 (38.6%)	185 (19.3%)	61 (12.8%)
Tx-related Grade 3 or 4 AE	9 (2.1%)	2 (0.5%)	3 (0.7%)	7 (1.6%)	3 (0.3%)	6 (1.3%)
Any SAE	37 (8.5%)	29 (6.7%)	33 (7.7%)	30 (6.9%)	42 (4.4%)	21 (4.4%)
Tx-related SAE	3 (0.7%)	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)
AE resulting in discontinuation	4 (0.9%)	6 (1.4%)	4 (0.9%)	7 (1.6%)	9 (0.9%)	7 (1.5%)
AE resulting in death	1 (0.2%)	0 (0.2%)	1 (0.2%)	2 (0.5%)	2 (0.2%)	0

Source: Table B-24, pp60-61; Table B-39, p77 of the submission

AE = adverse event; c = cobicistat; EVG = elvitegravir; FTC = emtricitabine; SAE = serious adverse event; TAF= tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; Tx = treatment

<sup>a</sup> Third agents: cobicistat + elvitegravir (~32%), efavirenz (~26%), ritonavir-boosted atazanavir (~15%), or cobicistat-boosted atazanavir (~27%)

- 6.11 The submission stated that EVG/c/FTC/tenofovir alafenamide offered benefits over EVG/c/FTC/tenofovir DF, or any other tenofovir DF-based regimen, in terms of increased bone mineral density and reduced renal function impact.
- 6.12 The decline in bone mineral density at the hip for EVG/c/FTC/tenofovir alafenamide treated patients was significantly smaller than the decline for EVG/c/FTC/tenofovir DF treated patients, with a difference of 2.29% (95% CI: 1.73% to 2.64%) for treatment-naïve patients and 2.08% (95% CI: 1.70% to 2.46%) for treatment-experienced patients. Although changes in hip bone mineral density were statistically significant at Week 48, these changes might not have been clinically relevant. The ESC considered that there was significant uncertainty that any measured benefits in terms of bone mineral density would result in clinically significant reduction in the risk of patient relevant outcomes such as fracture.
- 6.13 Changes in serum creatinine are presented in the table below.

**Table 5: Change in serum creatinine from baseline by visit in treatment-naïve and treatment-experienced patients (safety analysis sets)**

Treatment naïve	EVG/c/FTC/TAF		EVG/c/FTC/TDF		Difference in LSM (95% CI)
	N	Mean, mg/dL (SD)	N	Mean, mg/dL (SD)	
<b>Study 104</b>					
Baseline serum creatinine	435	0.91 (0.17)	432	0.93 (0.17)	-0.02 (-0.04, 0.00)
Δ at Week 2	417	0.07 (0.09)	422	0.10 (0.13)	<b>-0.03 (-0.05, -0.02)</b>
Δ at Week 24	418	0.07 (0.11)	417	0.10 (0.12)	<b>-0.03 (-0.05, -0.02)</b>
Δ at Week 48	415	0.08 (0.11)	404	0.11 (0.12)	<b>-0.03 (-0.04, -0.01)</b>
<b>Study 111</b>					
Baseline serum creatinine	431	0.95 (0.17)	435	0.94 (0.16)	0.01 (-0.02, 0.03)
Δ at Week 2	422	0.06 (0.12)	422	0.10 (0.12)	<b>-0.04 (-0.05, -0.02)</b>
Δ at Week 24	418	0.07 (0.12)	417	0.10 (0.12)	<b>-0.03 (-0.04, -0.01)</b>
Δ at Week 48	405	0.08 (0.14)	402	0.12 (0.28)	<b>-0.04 (-0.07, -0.01)</b>
Treatment experienced	EVG/c/FTC/TAF		FTC/TDF + 3 <sup>rd</sup> agent <sup>a</sup>		Difference in LSM (95% CI)
	N	Mean, mg/dL (SD)	N	Mean, mg/dL (SD)	
<b>Study 109</b>					
Baseline serum creatinine	708	1.05 (0.19)	352	1.05 (0.19)	-0.01 (-0.03, 0.02)
Δ at Week 2	678	0.00 (0.11)	331	0.01 (0.09)	<b>-0.02, (-0.03, -0.00)</b>
Δ at Week 24	687	0.00 (0.11)	335	0.02 (0.11)	<b>-0.03 (-0.04, -0.02)</b>
Δ at Week 48	545	-0.01 (0.12)	266	0.04 (0.12)	<b>-0.05 (-0.07, -0.03)</b>

Source: Table 46.2, pp542-548 of Study 104 CSR; Table 46.2, pp553-559 of Study 111 CSR; and Table 47.2, pp1,109-1,115 of Study 109 CSR

c = cobicistat; CI = confidence interval; EVG = elvitegravir; FTC = emtricitabine; LSM = least squares mean; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; **Bold** = significant result

<sup>a</sup> Third agents: cobicistat + elvitegravir (~32%), ritonavir-boosted atazanavir (~15%), or cobicistat-boosted atazanavir (~27%)

- 6.14 The submission stated that EVG/c/FTC/tenofovir alafenamide was associated with a preferential renal safety profile compared with EVG/c/FTC/tenofovir DF and FTC/tenofovir DF plus third agent regimens and demonstrated a significantly more favourable outcome in terms of change in serum creatinine. It should be noted that at Week 2 there was an initial difference in serum creatinine of approximately 0.03 mg/dL, which was maintained throughout the 48 week observation period. A similar trend was observed for estimated glomerular filtration rate (data not presented). Further, patients were included in the three pivotal trials if they had an estimated glomerular filtration rate of 50 mL/minute or above. The Australian product information for EVG/c/FTC/tenofovir DF recommends that treatment should not be

initiated in patients with an estimated glomerular filtration rate below 70 mL/minute. This might have resulted in poorer than expected renal outcomes for some patients in the EVG/c/FTC/tenofovir DF arms. The ESC agreed that there was significant uncertainty that any measured benefits in terms of renal function would result in clinically significant reduction in the risk in patient relevant outcomes like symptomatic renal failure.

### **Clinical claim**

- 6.15 The submission described EVG/c/FTC/tenofovir alafenamide as non-inferior in terms of comparative effectiveness and favourable in terms of comparative safety over EVG/c/FTC/tenofovir DF in treatment-naïve patients and non-inferior in terms of comparative effectiveness and safety over FTC/tenofovir DF plus third agent regimens in treatment-experienced patients.
- 6.16 The claims of non-inferiority in terms of comparative effectiveness in treatment-naïve and treatment-experienced patients were adequately supported.
- 6.17 The claim that EVG/c/FTC/tenofovir alafenamide had a favourable safety profile compared with EVG/c/FTC/tenofovir DF in treatment-naïve patients might be supported with respect to intermediate outcome measures relating to bone mineral density and renal function. However, it may have been more appropriate for the submission to have claimed non-inferiority in terms of comparative safety as:
- there were no significant differences in the rates of treatment-emergent adverse events or serious adverse events;
  - the benefits of EVG/c/FTC/tenofovir alafenamide in terms of bone mineral density were small and might not be clinically relevant. Further, follow-up was limited to 48 weeks, which might not reflect the long-term risk of fractures;
  - patients were included in Studies 104 and 111 if they had an estimated glomerular filtration rate of 50 mL/minute or above. The Australian product information for EVG/c/FTC/tenofovir DF recommends that treatment should not be initiated in patients with an estimated glomerular filtration rate below 70 mL/minute. This might have resulted in poorer than expected renal outcomes for some patients in the EVG/c/FTC/tenofovir DF arms; and
  - the differences in renal safety were based on the surrogate outcomes of serum creatinine, estimated glomerular filtration rates and proteinuria. Although statistically significant, it was unclear whether the results were clinically relevant. From the key trials it was unclear whether the differences between EVG/c/FTC/tenofovir alafenamide and EVG/c/FTC/tenofovir DF seen at Week 48 would be maintained and would result in lower long-term renal event rates.
- 6.18 The claim of non-inferiority of EVG/c/FTC/tenofovir alafenamide in terms of comparative safety to FTC/tenofovir DF plus third agent in treatment-experienced patients was adequately supported.
- 6.19 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable. In terms of comparative safety, the PBAC agreed with the ESC as stated in paragraph 6.14 above and that it was reasonable to accept non-inferior comparative safety against Stribild®.

## Economic analysis

- 6.20 The submission presented a cost-minimisation analysis.
- 6.21 The equi-effective doses were estimated as:
- elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (EVG/c/FTC/tenofovir alafenamide) in a FDC product, once daily; and
  - elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (EVG/c/FTC/tenofovir DF) in a FDC product, once daily.
- 6.22 The cost-minimisation analysis only included the cost of drug acquisition. The submission considered there would be no additional cost consequences of listing EVG/c/FTC/tenofovir alafenamide. This was reasonable.

**Table 6: Cost-minimisation analysis for EVG/c/FTC/tenofovir alafenamide FDC**

		Method	
<b>EVG/c/FTC/tenofovir DF FDC</b>			
-	PBS item code	—	10307L
A	AEMP (30 tablets/1 pack)	Submission	\$1,036.68
<b>EVG/c/FTC/tenofovir alafenamide FDC</b>			
B	AEMP (30 tablets/1 pack)	A	\$ [REDACTED]
C	Maximum quantity; packs	—	2
D	HSD mark-up (Private)	PBS Schedule	\$40 <sup>a</sup>
E	Dispensing fee		\$6.93 <sup>b</sup>
F	<b>Public hospital for DPMQ</b>	B x C	\$ [REDACTED]
G	<b>Private hospital/Community Access Program for DPMQ</b>	(D + E) + F	\$ [REDACTED]

Source: Table D.1, p95 of the submission; and calculated during the evaluation

AEMP = approved ex-manufacturer price; c = cobicistat; DF = disoproxil fumarate; DPMQ = dispensed price for maximum quantity; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; HSD = Highly Specialised Drug; PBS = Pharmaceutical Benefits Scheme

<sup>a</sup> For drugs with AEMP > \$1,000.00

<sup>b</sup> As of 1 July 2015, the ready-prepared dispensing fee is \$6.93

**Drug cost/patient/year: Public hospital - \$ [REDACTED];  
Private hospital/Community Access Program - \$ [REDACTED].**

- 6.23 Treatment with EVG/c/FTC/tenofovir alafenamide is ongoing. The annual drug costs were calculated using the dispensed price for maximum quantity for public hospital and private hospital/Community Access Program and assuming an average of 6.1 dispensings per patient per year (60 days treatment per dispensing). The annual costs of the comparator, EVG/c/FTC/tenofovir DF, are the same.

## Estimated PBS usage & financial implications

- 6.24 The submission used a market share approach to estimate the utilisation and cost of EVG/c/FTC/tenofovir alafenamide over a five year time horizon. The submission assumed that utilisation of EVG/c/FTC/tenofovir alafenamide was expected to be almost exclusively accounted for by patients switching from EVG/c/FTC/tenofovir DF, with minimal substitution of other HIV single tablet regimens. The ESC considered that if there are perceived safety benefits, EVG/c/FTC/TAF might substitute for other single tablet regimens and for other TDF-containing first line regimens.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Projected HIV single tablet services					
EVG/c/FTC/TAF uptake rate	7%	12%	17%	19%	21%
EVG/c/FTC/TAF services (2 packs)					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost saving to PBS/RPBS	-\$	-\$	-\$	-\$	-\$
Net cost to MBS	\$0	\$0	\$0	\$0	\$0
<b>Estimated total net cost</b>					
<b>Net cost to PBS/RPBS/MBS</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>

Source: 'ECFTAF PBAC submission\_Section E Workbook FINAL.xlsx'; and calculated during evaluation

c = cobicistat; EVG = elvitegravir; FTC = emtricitabine; HIV = human immunodeficiency virus; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; TAF = tenofovir alafenamide

- 6.25 It was estimated that there would be [REDACTED] dispensings (60 tablets) of EVG/c/FTC/tenofovir alafenamide FDC in Year 5 of listing. This corresponds to a net cost to the PBS/RPBS of approximately \$30 – \$60 million in Year 5 and of \$60 – \$100 million over the first five years.
- 6.26 The ESC noted it was unknown whether utilisation and cost estimates were an over or underestimation as:
- there was considerable uncertainty around the projected market for EVG/c/FTC/tenofovir alafenamide FDC, due to the use of a linear extrapolation to project HIV single tablet market growth (overestimation);
  - the assumed uptake rates for EVG/c/FTC/tenofovir alafenamide FDC were not justified (over or underestimation);
  - the proposed TGA indication for EVG/c/FTC/tenofovir alafenamide FDC includes adolescent patients and patents with mild to moderate renal failure. For those patients fewer single tablet options are available (underestimate); and
  - the impact of the Community Access Program to dispensing of HIV medications was not explored as data were not available to make projections regarding this (over or underestimation).
- 6.27 The submission estimated that the use of other HIV single tablet regimens would be expected to drop as a result of direct substitution with EVG/c/FTC/tenofovir alafenamide FDC. Overall the submission concluded that there would be no financial impact of the PBS listing of EVG/c/FTC/tenofovir alafenamide to the Commonwealth Government Health Budget.

### Request under Subsection 101(4AC) of the National Health Act 1953

- 6.28 The submission requested that the PBAC advice the Minister under Subsection 101(4AC) of the National Health Act 1953 to list EVG/c/FTC/tenofovir alafenamide FDC such that the price of EVG/c/FTC/tenofovir alafenamide FDC be maintained in the event of any future reductions in the price of genericised components of the FDC.

Section 101(4AC) of the Act states that:

*If the Committee is satisfied that the therapy involving a combination item provides, for some patients:*

(a) a significant improvement in patient compliance with the therapy; or  
(b) a significant improvement in efficacy or reduction in toxicity;  
over alternative therapies, then the Committee must advise the Minister accordingly.

- 6.29 The submission makes a claim on both improved compliance and improved efficacy or reduced toxicity.
- 6.30 The PBAC agreed with the DUSC that the claim of improved compliance over the alternative therapy nominated in the submission elvitegravir/cobicistat/emtricitabine/tenofovir DF (Stribild<sup>®</sup>) was not reliably demonstrated based on the following issues:
- Quantitative or qualitative evidence specifically comparing compliance with an EVG/c/FTC/tenofovir alafenamide single-tablet regimen to alternative therapy/s has not been provided. The claim in the submission is speculative in nature.
  - Quantitative or qualitative evidence demonstrating the impact of improved compliance on health outcomes specific to the EVG/c/FTC/tenofovir alafenamide single-tablet regimen over alternative therapy/s has not been provided.
  - The improvements in toxicity are based on small changes in surrogate markers for renal impairment and osteoporosis/osteopenia over a short timeframe (48 weeks).
  - The clinical relevance, nor the relevance to patients of the changes in surrogate endpoints, including over a life-time of therapy has not been substantiated.
- 6.31 The PBAC agreed with the ESC advice and noted the following points:
- EVG/c/FTC/tenofovir alafenamide met the definition of a combination product, which was appropriate;
  - the claim of minimised toxic effects over a lifetime of treatment, as EVG/c/FTC/tenofovir alafenamide had less impact on surrogate endpoints related to renal and bone safety. This might not have been appropriate, as it was difficult to quantify differences in effects seen at Week 48 in terms of long-term outcomes; and
  - the submission provided features that were likely to facilitate improved treatment compliance for some patients over a multiple tablet regimen. This was not appropriate as the submission did not provide evidence of improved compliance.
- 6.32 The PBAC also agreed with the ESC and considered that patient relevant safety benefits of EVG/c/FTC/tenofovir alafenamide over EVG/c/FTC/TDF were uncertain, and furthermore that safety benefit over non-TDF containing highly active antiretroviral therapies (e.g ABC/3TC/DTG) was not demonstrated. In addition, there was no reason to expect any benefit in compliance over existing highly active low pill burden ARV therapies.
- 6.33 The Pre-Sub-Committee Response argued that it is not a requirement of the Act to provide evidence to support this claim as the request relies on PBAC's determination. The ESC considered there was insufficient evidence to support a claim that EVG/c/FRC/TAF offered a substantial benefit in terms of efficacy, safety, or compliance over existing PBS-listed products. The PBAC agreed with the ESC.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended Section 100 Highly Specialised Drugs Program (HSD) listing of elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide (EVG/c/FTC/tenofovir alafenamide) fixed dose combination for the treatment of HIV. The PBAC recommended the special arrangements under the HSD Community Access, Authority Required (STREAMLINED).
- 7.2 The PBAC recommended the listing of EVG/c/FTC/tenofovir alafenamide on a cost-minimisation basis with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild<sup>®</sup>). The equi-effective doses are elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg in a FDC product, once daily is equal to elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (EVG/c/FTC/tenofovir DF) in a FDC product, once daily.
- 7.3 The PBAC recommended that the restriction for EVG/c/FTC/tenofovir alafenamide should be consistent with that of Stribild<sup>®</sup>, and that it therefore include both treatment-experienced and treatment-naïve patients.
- 7.4 The PBAC accepted elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild<sup>®</sup>) as the most appropriate comparator. The PBAC agreed with ESC that EVG/c/FTC/tenofovir alafenamide might also displace other TDF/FTC-containing single tablet and multi-tablet highly active antiretroviral therapies as well as dolutegravir/abacavir/lamivudine FDC (Triumeq<sup>®</sup>) for adolescents and patients with renal impairment.
- 7.5 The PBAC noted that the primary trials (Study 104 and Study 111) and supplementary trial (Study 109) reported the proportion of patients with HIV ribonucleic acid (RNA) < 50 copies/mL as the clinically relevant outcome. The PBAC also noted that in terms of safety, there were similar rates of adverse events and serious adverse events in treatment-naïve patients (Studies 104 and 111). The PBAC agreed that EVG/c/FTC/tenofovir alafenamide was non-inferior to EVG/c/FTC/tenofovir DF in comparative efficacy and safety.
- 7.6 The PBAC noted the submission's utilisation estimates and claim of cost neutrality to the Commonwealth Government Health Budget as reported in paragraphs 6.24 to 6.26. The PBAC agreed with ESC that if there are perceived safety benefits, EVG/c/FTC/TAF might substitute for other single tablet regimens and for other TDF-containing first line regimens.
- 7.7 **Advice to the Minister under subsection 101(4AC) of the Act**  
The PBAC noted the submission requested that the PBAC advise the Minister under subsection 101(4AC) of the Act. Based on the reasons provided in paragraphs 6.30 to 6.32, the PBAC decided it was not satisfied as required by subsection 101(4AC) and therefore will not provide advice to the Minister under that section.
- 7.8 The PBAC advised that Section 100 medicines are currently considered out of scope by prescribing by nurse practitioners.

- 7.9 The PBAC recommended that the Safety Net 20 Day Rule should apply to EVG/c/FTC/tenofovir alafenamide. The PBAC also recommended that the Safety Net rule should flow-on to all HIV treatment currently listed on the PBS.
- 7.10 In accordance with subsection 101(3BA) of the Act, the PBAC advised that it is of the opinion that EVG/c/FTC/tenofovir alafenamide should not be treated as interchangeable on an individual patient basis with other antiretroviral therapies.

**Outcome:**

Recommended

**8 Recommended listing**

- 8.1 Add new item: Safety Net 20 Day rule to flow-on to all HIV treatment currently listed on the PBS.

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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ELVITEGRAVIR + COBICISTAT + EMTRICITABINE + TENOFOVIR ALAFENAMIDE fixed dose combination tablet 60, elvitegravir 150mg +cobicistat 150 mg +emtricitabine 200mg +tenofovir alafenamide 10mg	60	5	TBA	Gilead Sciences Pty Ltd

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program (Community Access)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	HIV Infection
<b>PBS Indication:</b>	HIV Infection
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must be antiretroviral treatment naïve.

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program (Community Access)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	HIV Infection
<b>PBS Indication:</b>	HIV Infection
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised therapy for HIV infection.

**9 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.

**10 Sponsor's Comment**

The sponsor had no comment.