

## 5.12 TENOFOVIR ALAFENAMIDE/EMTRICITABINE, TABLET, TENOFOVIR ALAFENAMIDE 10 OR 25MG AND EMTRICITABINE 200MG, DESCOVY®, GILEAD SCIENCES PTY LTD.

### Preface

To improve the readability of this document, brand names are generally used to identify fixed dose combination (FDC) antiretroviral products. Where the form of the drug within a brand is described, the Public Summary Document uses the Australian Medicines Terminology medicinal product unit of use (MPUU).

FDC of antiretroviral therapies	Drug classes	Brand name
<b>Single tablet regimens</b>		
Rilpivirine/emtricitabine/ <b>tenofovir alafenamide</b>	NNRTI/NRTI/NRTI	Odefsey®
Rilpivirine/emtricitabine/tenofovir disoproxil fumarate	NNRTI/NRTI/NRTI	Eviplera®
Efavirenz/emtricitabine/tenofovir disoproxil fumarate	NNRTI/NRTI/NRTI	Atripla®
Dolutegravir/abacavir/lamivudine	INSTI/NRTI/NRTI	Triumeq®
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	INSTI/PK enhancer/NRTI/NRTI	Stribild®
Elvitegravir/cobicistat/emtricitabine/ <b>tenofovir alafenamide</b>	INSTI/PK enhancer/NRTI/NRTI	Descovy®
<b>NRTI backbones</b>		
Emtricitabine/ <b>tenofovir alafenamide</b>	NRTI/NRTI	Descovy®
Emtricitabine/tenofovir disoproxil fumarate	NRTI/NRTI	Truvada®
Abacavir/lamivudine	NRTI/NRTI	Kivexa®

### 1 Purpose of Application

- 1.1 Section 100 Highly Specialised Drug Program (Community Access): Authority Required (Streamlined) listing for two strengths of the Descovy® (emtricitabine 200 mg + tenofovir alafenamide 25 mg or 10 mg) fixed-dose combination, for treatment of human immunodeficiency virus (HIV) for treatment-naïve patients and treatment-experienced patients.

### 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	DPMQ	Proprietary Name and Manufacturer	
EMTRICITABINE + TENOFOVIR ALAFENAMIDE emtricitabine 200mg + tenofovir alafenamide 25mg, tablet	60	5	\$1,500.63	Descovy®	Gilead Sciences Pty Ltd
emtricitabine 200mg + tenofovir alafenamide 10mg, tablet	60	5	\$1,500.63	Descovy®	Gilead Sciences Pty Ltd
Category / Program	Section 100 – Highly Specialised Drugs Program (Community Access)				
Condition	HIV infection				
Restriction	Authority Required (Streamlined)				
Treatment criteria	Treatment phase: Initial				
Clinical criteria	Patient must be antiretroviral treatment naïve AND The treatment must be in combination with other antiretroviral agents				
Category / Program	Section 100 – Highly Specialised Drugs Program (Community Access)				
Condition	HIV infection				

Restriction	Authority Required (Streamlined)
Treatment criteria	Treatment phase: Continuing
Clinical criteria	Patients must have previously received PBS-subsidised therapy for HIV infection AND The treatment must be in combination with other antiretroviral agents

- 2.1 The submission provided a cost-minimisation analysis of Descovy® versus the nominated comparator Truvada® based on drug cost only.
- 2.2 On the basis of a claim of favourable safety, the Sponsor requested that the PBAC provide advice to the Minister under Section 101(4AC) of the *National Health Act 1953* (the Act).

### 3 Background

- 3.1 TGA status at time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC, Descovy had been registered. The approved TGA indication was: “DESCOVY is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of DESCOVY”... “DESCOVY is not for use in Pre-Exposure Prophylaxis (PrEP).”
- 3.2 This is the first submission requesting PBS-listing of Descovy®. A concurrent submission seeking PBS-listing of a FDC Odefsey® was considered at the July 2016 PBAC meeting.
- 3.3 Truvada® was recommended by the PBAC in November 2005 on the basis of a cost-minimisation analysis to the individual components.
- 3.4 Genvoya® was recommended by the PBAC in November 2015 on the basis of a cost-minimisation analysis to Stribild®. On the basis of a claim of favourable safety, the Sponsor requested that the PBAC provide advice under Section 101(4AC) of the Act. The PBAC decided it was not satisfied as required by subsection 101(4AC).

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### 4 Clinical place for the proposed therapy

- 4.1 An antiretroviral therapy (ART) regimen for a treatment-naive HIV-positive patient generally consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), one of which is emtricitabine or lamivudine, plus an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor with a pharmacokinetic enhancer. The Australian commentary on the US Department of Health and Human Services Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (2015) by the Australasian Society for HIV Medicine (ASHM) has ‘recommended’, ‘alternative’, and ‘other’ regimens. The guidelines recommend expert advice in assessing and managing a treatment-experienced patient experiencing ART failure. A new regimen should include at least two, preferably three, fully active agents.

- 4.2 The submission proposed that Descovy® will provide an alternative NRTI backbone to Truvada®, particularly in patients with chronic renal disease or osteoporosis, and would not otherwise change the clinical management algorithm. The Descovy® dual NRTI backbone would also provide the ability to preserve the same NRTI backbone and change the third antiretroviral in the regimen where warranted by the resistance profile in treatment-experienced patients.

## **5 Comparator**

- 5.1 The submission nominated Truvada® as the comparator.
- 5.2 The evaluation and ESC advised that this was an appropriate comparator for adult patients but that in adolescents, the other main NRTI backbone drug Kivexa® (abacavir 600 mg/lamivudine 300 mg) might be the more appropriate comparator as Truvada® is not TGA indicated for adolescents and patients with creatinine clearance below 70 mL/minute (Australian Product Information).
- 5.3 The PBAC accepted that Truvada® was the appropriate comparator as current prescribing algorithms suggests it would unlikely substitute for non TDF-containing dual NRTI regimens such as Kivexa®.

*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 is based on one Phase III head-to-head randomised-controlled 'switch' trial comparing Descovy® versus Truvada®, plus a third agent, in virologically suppressed HIV-positive patients on Truvada®-based regimens (Study 1089). A  $\pm 10\%$  margin was used to assess non-inferior efficacy.
- 6.4 The submission also presented five supportive/supplementary trials/studies:
- Two bioequivalence studies comparing Descovy® with Genvoya® in healthy volunteers (Studies 1472 and 1473).
  - Two supplementary Phase III randomised controlled trials comparing Genvoya® to Stribild® in treatment-naïve patients (Studies 104 and 111). These trials were previously considered by the PBAC during its consideration of the November 2015 Genvoya® submission. The current submission provided additional longer term data (to 96 weeks, 48 week data was considered previously), which was used to

support a claim of a favourable safety profile of tenofovir alafenamide versus tenofovir disoproxil fumarate.

- One supplementary open-label single-arm cohort study of Genvoya® in treatment-naïve and treatment-experienced patients with mild to moderate renal impairment (Study 112). This was included the November 2015 Genvoya® submission as a supplementary study. The submission provided a poster presentation with longer term data (to 96 weeks) from Study 112.

6.5 The submission stated on the basis that the emtricitabine and tenofovir alafenamide components of Descovy® and Genvoya® were bioequivalent, consideration of the Genvoya® versus Stribild® trials and Genvoya® cohort study is justified. Evidence was not presented to support the bioequivalence of the emtricitabine and tenofovir disoproxil fumarate components of Truvada® and Stribild® to support the relevance of the trials to the nominated comparator of Truvada®.

6.6 Details of the trials presented in the submission are provided in Table 1.

**Table 1: Trials and associated reports presented in the submission**

<b>Trial ID/First Author</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Key randomised controlled trial</b>		
<b>Study 1089</b> NCT02121795 GS-US-311-1089	A Phase 3, Randomised, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens Containing Truvada. Interim Week 48 Clinical Study Report. <i>Gallant JE, Daar ES, Raffi Fs, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial.</i>	22 September 2015 (revised 13 November 2015)  <i>Lancet HIV 2016; published online 14 March 2016</i> <a href="http://dx.doi.org/10.1016/S2352-3018(16)00024-2">http://dx.doi.org/10.1016/S2352-3018(16)00024-2</a>
<b>Bioequivalence studies</b>		
<b>Study 1472</b> GS-US-311-1472	A Phase 1, Randomised, Open-label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir Alafenamide (200/10mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10mg) Fixed-Dose Combination Tablets. Final Clinical Study Report	23 December 2014
<b>Study 1473</b> GS-US-311-1473	A Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir Alafenamide (200/25 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets. Final Clinical Study Report.	16 December
<b>Supplementary randomised controlled trials</b>		
<b>Study 104</b> NCT01780506 GS-US-292-0104	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-Naive Adults. Interim Week 48 Clinical Study Report. A Phase 3, Randomised, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir	6 October 2014  2 October 2015

Trial ID/First Author	Protocol title/ Publication title	Publication citation
	Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults. Interim Week 96 Clinical Study Report. Sax PE, Whol D, Yin MT, <i>et al.</i> 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. <i>Wohl D, Oka S, Clumeck N, et al. A Randomized, Double-Blind comparison of Tenofovir Alafenamide (TAF) vs. Tenofovir Disoproxil fumarate (TDF), each coformulated with Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for initial HIV-1 Treatment: Week 96 results.</i>	<i>Lancet</i> 2015; 385 (9987): 2606-2615.  <i>J Acquir Immune Defic Syndr</i> 2016 [Epub ahead of print]
<b>Study 111</b> NCT01797445 GS-US-292-0111	A Phase 3, Randomized, 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-Naive Adults. Interim Week 48 Clinical Study Report.	13 October 2014
	A Phase 3, Randomized, 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-Naive Adults. Interim Week 96 Clinical Study Report. Sax PE, Whol D, Yin MT, <i>et al.</i> 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.	2 October 2015  <i>Lancet</i> 2015; 385 (9987): 2606-2615.
<b>Supplementary open-label cohort study</b>		
<b>Study 112</b> NCT01818596 GS-US-292-0112	A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment. Interim Week 24 Clinical Study Report.	13 October 2014

Source: Table B.5, pp39-40 of the submission

6.7 The key features of the randomised trials and studies are summarised in Table 2.

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

Trial / Study	N	Design/ duration	Risk of bias	Patient population	Intervention	Key outcome(s)
<b>Key randomised controlled trial (Phase III)</b>						
Study 1089	668	R, DB, MC, 48wks (96 wks ongoing)	Low	HIV-1 positive; treatment-experienced virologically suppressed on Truvada®	Descovy® + 3 <sup>rd</sup> agent vs Truvada® + 3 <sup>rd</sup> agent	% with HIV RNA <50 copies/mL at week 48
<b>Bioequivalence studies (Phase I)</b>						
Study 1472	100	R, OL, CO, SD, 7days w/o	Low	Healthy volunteers 18-45 years	Descovy® (10mg) + elvitegravir + cobicistat vs Genvoya®	PK parameters
Study 1473	116	R, OL, CO, SD, 7days w/o	Low	Healthy volunteers 18-45 years	Descovy® (25mg) vs Genvoya®	PK parameters
<b>Supplementary RCTS (Phase III)</b>						
Study 104	872	R, DB, MC, 96wks (144wks ongoing)	Low	HIV-1 positive; treatment naïve	Genvoya® versus Stribild®	% with HIV RNA <50 copies/mL at week 48
Study	872	R, DB, MC,	Low	HIV-1 positive; Treatment	Genvoya® versus	% with HIV RNA

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Trial / Study	N	Design/ duration	Risk of bias	Patient population	Intervention	Key outcome(s)
111		96wks (144wks ongoing)		naïve	Stribild®	<50 copies/mL at week 48
<b>Supplementary cohort study (Phase III)</b>						
Study 112	252	OL, MC, <u>cohort</u> , 96wks	NA	HIV-1 positive; treatment experienced virologically suppressed and treatment naïve; eGFR 30-69 mL/min	Genvoya®	% with HIV RNA <50 copies/mL at week 24; Change from baseline in eGFR <sup>a</sup> at week 24

Source: constructed during the evaluation

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; P=phase; SD= single dose; w/o=wash out; CO=cross-over

<sup>a</sup> calculated using the Cockcroft-Gault equation, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum cystatin C method and CKD-EPI serum creatinine method respectively

Note: Allowed 3<sup>rd</sup> agents in Study 1089 were atazanavir + ritonavir, lopinavir + ritonavir, darunavir + ritonavir, efavirenz, rilpivirine, nevirapine, raltegravir, dolutegravir and maraviroc. Descovy® contains emtricitabine 200mg/ tenofovir alafenamide 25 mg or 10 mg. Truvada® contains emtricitabine 200 mg/ tenofovir disoproxil fumarate 300mg. Odefsey® contains rilpivirine 25 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg. Genvoya® contains elvitegravir 150 mg/ cobicistat 150 mg/ emtricitabine 200 mg/ tenofovir alafenamide 10 mg. Stribild® contains elvitegravir 150 mg/ cobicistat 150 mg/ emtricitabine 200mg/ tenofovir disoproxil fumarate 300mg.

## Comparative effectiveness

**Table 3: Proportion of patients with HIV RNA <50 copies/mL at Week 48 using the FDA snapshot algorithm (full analysis set) in treatment-experienced patients (Study 1089)**

	% with HIV RNA <50 copies/mL; n/N (%)		Difference in % (95.002% CI) <sup>a</sup>
	Descovy® + 3 <sup>rd</sup> agent	Truvada® + 3 <sup>rd</sup> agent	
Overall population	314/333 (94.3)	307/330 (93.0)	1.3 (-2.5, 5.1)

Abbreviations: FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate;

Source: TableB.21, p68 of the submission

<sup>a</sup> Difference in percentages of virologic success between treatment groups and its 95.002% CI were calculated based on the Mantel-Haenszel proportions adjusted by the third agent stratum.

Note: Descovy® contains emtricitabine 200 mg/ tenofovir alafenamide 25 mg or 10 mg. Truvada® contains emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg. No virologic data in Week 48 window for 2 subjects (2.7%) in the Descovy® + nevirapine arm (*discontinued due to AE/death and discontinued due other reasons*) and 1 subject (1.5%) in the Truvada® + nevirapine arm (*discontinued due to other reasons*). One subject each in the Truvada® + rilpivirine and Truvada® + efavirenz arms experienced virological failure at Week 48.

- 6.8 For the overall population of Study 1089, the submission stated that switching to Descovy® plus a third agent was non-inferior to maintaining Truvada® plus a third agent at 48 weeks, as the lower bound of the two-sided 95.002% CI for the difference in response rate (-2.5%) was greater than the pre-specified non-inferiority margin of -10%. The per protocol (PP) analysis also supported the conclusion of non-inferiority, as the lower bound of the 95.002% CI was also greater than the pre-specified non-inferiority margin. Both the full analysis set and PP analyses met the pre-specified non-inferiority margin in Study 1089 of -10%; similarly both analyses also met the more stringent FDA non-inferiority threshold of -4%.
- 6.9 In the bioequivalence studies, the 90% CIs for all of the GLSM ratios of the pharmacokinetic parameters for emtricitabine and tenofovir alafenamide fell within the pre-specified boundary of 80% to 125% in both bioequivalence trials. The submission concluded that the emtricitabine and tenofovir alafenamide components of Descovy® (tenofovir alafenamide 10 mg presentation taken concomitantly with elvitegravir 150 mg and cobicistat 150 mg and the tenofovir alafenamide 25 mg presentation taken alone) are bioequivalent to Genvoya®. The results support these conclusions.
- 6.10 The primary outcome in the supplementary Genvoya® trials/studies was also the proportion of patients with HIV RNA <50 copies at 48 weeks (FDA snapshot algorithm). Results at 98 weeks was a secondary outcome (Study 104: RD=1.3%, 95%CI: -2.9, 5.5; Study 111: RD=1.7%, 95% CI: -3.3, 6.8). In 112, 214/242 (88%) of the treatment experienced patients (“cohort 1”) had HIV RNA <50 copies/mL at Week 96, down from 230/242 (95%) at Week 24.

## Comparative harms

- 6.11 The safety data from the entire trial population of Study 1089 was informative, and the supplementary trials using Genvoya® (Studies 104 and 111), appeared broadly informative given that two of the components of Descovy® (emtricitabine and tenofovir alafenamide) were administered. However, the basis of the selection of supplementary trials was unclear as there appeared to be other trials with tenofovir alafenamide being conducted or completed.

- 6.12 A similar proportion of patients experienced any treatment-emergent adverse event between arms within Studies 1089, 104 and 111; and discontinuation of study drug due to an adverse event was infrequent. Commonly reported treatment-emergent adverse events included diarrhoea, nausea, upper respiratory tract infection, nasopharyngitis, headache, back pain and arthralgia. The incidence of adverse events was higher in Studies 104 and 111 compared with Study 1089, which is consistent with treatment-naïve versus treatment-experienced populations, longer duration of follow-up in Studies 104 and 111, and may or may not be related to the different ART regimens.
- 6.13 One patient died in Study 1089 due to lymphoma, three in Study 104 due to embolic stroke, cardiac arrest and lung non-small cell carcinoma, and three patients died in Study 111 due to alcohol intoxication, myocardial infarction and recreational drug overdose; none of the deaths were considered related to the study drug.
- 6.14 Adverse events and laboratory abnormalities related to lipids were more commonly reported in the tenofovir alafenamide arms (Descovy® and Genvoya®) compared to the tenofovir disoproxil fumarate arms (Truvada® and Stribild®) in Studies 1089, 104 and 111, however they were generally non-serious and rarely led to discontinuation. The submission stated that while the change in lipid profiles was statistically significant with a greater increase in median values in the tenofovir alafenamide arm, the clinical relevance of this finding is unclear. The PBAC indicated that the lipid abnormalities may be relevant as a risk factor for future cardiac events, but from the limited short term data provided the PBAC is uncertain as to the clinical significance of these results.
- 6.15 The submission claimed that tenofovir alafenamide was associated with a favourable safety profile over tenofovir disoproxil fumarate on the basis of parameters associated with renal and bone toxicities.
- 6.16 At its November 2015 meeting, the PBAC recommended that Genvoya® was non-inferior to Stribild® in terms of comparative efficacy and safety on the basis of 48 weeks of safety data. The additional 96 week safety data from Studies 104 and 111 provided in this submission still mostly related to surrogate markers of renal impairment and osteoporosis/ osteopenia. While there were some data on renal events and fractures, the low event rates precluded meaningful analyses. The submission did not adequately address the uncertainty of patient relevant safety benefits of Genvoya® over Stribild®, and by inference tenofovir alafenamide over tenofovir disoproxil fumarate, which is then applied to the comparison of Descovy® versus Truvada®.
- 6.17 The submission still did not provide evidence of comparative safety versus non-tenofovir disoproxil fumarate containing highly active antiretroviral therapies.
- 6.18 There were limited long-term safety data of ARTs regimens containing tenofovir alafenamide.

**Clinical claim**

- 6.19 The submission described Descovy® as non-inferior in terms of comparative effectiveness and “favourable” in terms of comparative safety over Truvada® on the basis of renal and bone related toxicity.
- 6.20 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.21 The PBAC considered that the claim of “favourable” comparative safety was not adequately supported by the data. In forming its view, the PBAC recalled its recommendation at its meeting of November 2015 to list Genvoya® and noted that at that time it had considered 48 weeks of safety data. The Descovy® submission includes the same data plus an additional 48 weeks of longer term safety data (total of 96 weeks). However PBAC remained of the view that it was difficult to discern any clinically meaningful safety advantage/s Genvoya® had over Stribild® and by inference tenofovir alafenamide over tenofovir disoproxil fumarate.

**Economic analysis**

- 6.22 The submission presented a cost-minimisation analysis.
- 6.23 Given the recommended dose of tenofovir alafenamide is based on the concomitant administration of a pharmacokinetic booster in the anti-retroviral therapy regimen, the equi-effective doses are estimated as:
  - Descovy® (emtricitabine 200 mg / tenofovir alafenamide 10 mg) in a pharmacokinetic boosted regimen;
  - Descovy® (emtricitabine 200 mg / tenofovir alafenamide 25 mg) in an un-boosted pharmacokinetic regimen;
  - Truvada® (emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg), regardless of boosted or unboosted pharmacokinetic regimen.

The PBAC accepted these equi-effective doses.

- 6.24 The submission presented a cost-minimisation analysis based on drug cost only. No differences were assumed in the utilisation of other healthcare resources.

**Table 4: Cost-minimisation analysis for Descovy® FDC (HSD Community Access)**

	Unit	AEMP/unit (April 2016)	Wholesale mark-up	PtP / unit	Max Qty	PtP/ Max Qty	Pharmacy Mark up	Dispense fee	DPMQ
Truvada®	1 box (30 tablets)	\$726.85	0.00	\$726.85	2	\$1,453.70	\$40.00	\$6.93	\$1,500.63
Descovy® 200/10 mg	1 box (30 tablets)	\$726.85	0.00	\$726.85	2	\$1,453.70	\$40.00	\$6.93	
Descovy® 200/25 mg	1 box (30 tablets)	\$726.85	0.00	\$726.85	2	\$1,453.70	\$40.00	\$6.93	

Source: Table D.1, p137 of the submission

Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = Dispensed Price for Maximum Quantity; max qty = maximum quantity; PtP = price to pharmacist

**Drug cost/patient/year: \$9,128.83**

6.25 The drug cost per patient per year of both Descovy® and Truvada® was calculated as \$9,128.83. Treatment with ARTs, including Descovy® and Truvada®, is ongoing. The drug cost per patient per year was calculated assuming 6.083 (=365/60) services per year and a dispensed price for maximum quantity of \$1,500.63 per 60 tablets.

**Estimated PBS usage & financial implications**

6.26 This submission was not considered by DUSC.

The submission used a market share approach, assuming pack-for-pack substitution of Descovy® for Truvada® from its projected market. The submission assumed that there was no additional growth of the Truvada® market due to the PBS-listing of Descovy®.

**Table 5: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number of Truvada® services					
Descovy® market share	50%	75%	85%	85%	85%
Number of Descovy® services					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost-offset from Truvada®	\$	\$	\$	\$	\$
<b>Estimated total net cost</b>					
<b>Net cost to PBS/RPBS/MBS</b>	\$0	\$0	\$0	\$0	\$0

Source: Descovy PBAC submission\_Section E Workbook.xlsx; Tables E.3, E.4, E.5 and E.6, pp143-146 of the submission

The redacted table shows that, at Year 5, the estimated number of Truvada and Descovy services was 50,000 – 100,000.

6.27 The submission estimated that the listing of Descovy® would be cost neutral for the government due to the identical price and straightforward pack-for-pack substitution of Descovy® for Truvada®.

6.28 The key areas of uncertainty in the estimates include:

- Should Descovy® substitute for Kivexa® there will be a net cost to the PBS at the requested price from the day of listing given the price of Kivexa® is significantly less.
- The number of prescriptions/year is a likely overestimate as a significant rate of growth was incorrectly calculated.

**Quality Use of Medicines**

6.29 The submission claimed that benefit of the lessened impact of therapy on parameters associated with renal and bone toxicities meets an important unmet need for the optimisation of long-term treatment in an aging cohort of HIV infected individuals who now have a life-expectancy close to that observed in the general population, and are therefore exposed to antiretroviral drugs for long periods of time. However, the data

provided in the submission relate to surrogate markers for renal impairment and osteoporosis or osteopenia over a relatively short duration, not long-term patient relevant outcomes (e.g. renal failure and fractures).

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

- 6.30 The submission requested that the PBAC advise the Minister under Subsection 101(4AC) of the National Health Act 1953 to list tenofovir alafenamide/emtricitabine FDC such that the price of tenofovir alafenamide/ emtricitabine 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.*

- 6.31 The submission claimed that Descovy® significantly reduced toxicity for some patients compared to Truvada®.
- 6.32 The submission stated that the claimed safety benefits of tenofovir alafenamide over tenofovir disoproxil fumarate was due to the lower systemic tenofovir exposure associated with tenofovir alafenamide (stated as 90% less than tenofovir disoproxil fumarate). The 96 week safety data from the supplementary trials (Studies 104 and 111) provided by the submission still related to surrogate markers of renal impairment and osteoporosis/osteopenia. The submission did not adequately address the uncertainty of patient relevant safety benefits of Genvoya® over Stribild® or Descovy® over Truvada®, and by inference tenofovir alafenamide over tenofovir disoproxil fumarate. The submission did not provide evidence of comparative safety versus non-tenofovir disoproxil fumarate containing ART regimens.
- 6.33 As noted at paragraphs 6.17 and 6.22 above, the PBAC considered there remained uncertainty that changes in surrogate outcomes of bone and renal safety at Week 96 are sufficient to support the claim of significant reduction in toxicity in some patients over a lifetime.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation on whether tenofovir alafenamide with emtricitabine should be listed in the Pharmaceutical Benefits Schedule for the treatment of HIV infection.
- 7.2 The PBAC deferred making a recommendation, noting that before doing so it wishes to hear the Department's views on matters relevant to the question of whether tenofovir disoproxil and tenofovir alafenamide should be declared as different drugs for the purposes of the Act, rather than as tenofovir, as currently. The PBAC noted that the Department is progressing its view about those matters, and that they are

matters with implications beyond Descovy®, Truvada® and related products. The PBAC requested the Department provide its views about those matters to the next regular meeting of the PBAC, so that the listing of Descovy® can be further considered in light of those views, and the position put by the Sponsor in its submission.

- 7.3 The PBAC formed the view that Descovy® (emtricitabine 200 mg + tenofovir alafenamide 10 mg or 25 mg tablet) is non inferior to Truvada® (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg tablet) in terms of effectiveness and safety. The equi-effective doses are:
- Descovy® (emtricitabine 200 mg / tenofovir alafenamide 10 mg) in a pharmacokinetic boosted regimen;
  - Descovy® (emtricitabine 200 mg / tenofovir alafenamide 25 mg) in an un-boosted pharmacokinetic regimen; with
  - Truvada® (emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg), regardless of boosted or unboosted pharmacokinetic regimen.
- 7.4 The PBAC noted that the primary trial (Study 1089) 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, a similar proportion of patients experienced any treatment-emergent adverse event between arms within Studies 1089, 104 and 111. The PBAC noted that this data was informative and considered Descovy® to be non-inferior to Truvada® in comparative efficacy and safety.
- 7.5 The PBAC considered the sponsor's request to have the restrictions for Truvada® to also apply to a listing of Descovy® to be appropriate. The PBAC formed the view that the Early Supply Rule should apply to Descovy®, as recommended for all HIV treatments at the November 2015 meeting.

#### **Advice to the Minister under subsection 101(4AC) of the Act**

- 7.6 The PBAC noted the submission requested that the PBAC advise the Minister under subsection 101(4AC) of the Act. Based on the reasons provided above, 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.

#### **Outcome:**

Deferred

### **8 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.

**9 Sponsor's Comment**

The sponsor had no comment.