5.13 TENOFOVIR ALAFENAMIDE, EMTRICITABINE AND RILPIVIRINE , fixed-dose combination tablet, tenofovir alafenamide 25 mg, emtricitabine 200 mg and rilpivirine 25 mg, Odefsey®, 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
Single tablet regimens		
Rilpivirine/emtricitabine/**tenofovir alafenamide**	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/**tenofovir alafenamide**	INSTI/PK enhancer/NRTI/NRTI	Genvoya®
NRTI backbones		
Emtricitabine/**tenofovir alafenamide**	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 Drugs Program (Community Access): Authority Required (Streamlined) listing for Odefsey® for the 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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RILPIVIRINE + EMTRICITABINE + TENOFOVIR ALAFENAMIDE rilpivirine 25mg + emtricitabine 200mg + tenofovir alafenamide 25mg tablet, 30	2	5	$2,043.79	Odefsey® 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.
Category/Program	Section 100 – Highly Specialised Drugs Program (Community Access)
Condition	HIV infection
Restriction	Authority Required (Streamlined)
Treatment criteria	Treatment Phase: Continuing
Clinical criteria	Patient must have previously received PBS-subsidised therapy for HIV infection.

2.1 The submission provided a cost-minimisation analysis of Odefsey® versus the nominated comparator Eviplera® based on drug cost only.

2.2 On the basis of a claim of favourable safety and compliance, the Sponsor requested that the PBAC gives advice to the Minister under Section 101(4AC) of the *National Health Act* 1953 (the Act).

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

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 consideration, the TGA Delegate's overview and clinical evaluation report were available.

3.2 This is the first submission requesting PBS-listing of Odefsey®. A concurrent submission seeking PBS-listing of a FDC containing Descovy® was considered at the July 2016 PBAC meeting.

3.3 Eviplera® was recommended by the PBAC in November 2011 on the basis of a cost-minimisation analysis compared with the Atripla®.

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).

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 Eviplera® which has an NNRTI as the third agent, is an 'alternative' regimen for patients with pre-treatment HIV ribonucleic acid (RNA) <100,000 copies/mL and CD4 T-lymphocytes (CD4 cell) count >200 cells/mm^3. The submission stated that Odefsey® would substitute for Eviplera®.

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

5 Comparator

5.1 Eviplera®. The PBAC noted that there are a number of single tablet fixed dose combination medicines listed on the PBS for HIV which Odefsey could potentially replace including Atripla®, but agreed with the pre-PBAC response that both Odefsey and Eviplera are distinct from the other PBS-listed single tablet fixed dose combination medicines with regard to a maximum limit for baseline viral load and requirement for dosing with meals, which means that they are unlikely to be widely prescribed in place of other single tablet fixed dose combination medicines to which this requirement does not apply.

5.2 The submission also nominated multi-tablet ART regimens without tenofovir alafenamide in the NRTI backbone as 'alternative therapies' for the purposes of the request under Subsection 101(4AC) of the Act. The submission further refined the definition of the NRTI backbone to the abacavir plus lamivudine FDC (Kivexa®) and emtricitabine plus tenofovir disoproxil fumarate FDC (Truvada®), with Truvada® being suitable for patients with a HLA-B*5701 allele (which increases the risk of hypersensitivity reactions to abacavir). The main arguments provided were that the requirement of the Act draws a distinction between 'therapy involving a combination item' and 'alternative therapies', which was interpreted as requesting a comparison of the combination product versus alternative therapies that do not meet the definition of a combination product (i.e. multi-tablet regimens). The submission further argued that the alternative therapies were multi-tablet regimens with NRTI backbones excluding tenofovir alafenamide, as tenofovir alafenamide is not available as a single-entity agent. The evaluation noted that the submission's claim that other single tablet fixed dose combination products cannot be considered as "alternative therapies" for the purposes of Section 101(4AC) is incorrect. The PBAC has previously considered other combination products as alternative therapies when providing advice under subsection 101(4AC) of the Act (see for example PBAC Public Summary for Vytorin® November 2014).

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 No head-to-head studies providing a comparison of Odefsey® and Eviplera® were available.

6.4 The submission was based on five trials/studies:

- 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 ±10% margin was used to assess non-inferior efficacy. The submission presented ad hoc subgroup analyses of patients using nevirapine, efavirenz and rilpivirine as the third agent. The submission acknowledged the small patient numbers using rilpivirine (as the third agent in this trial (Descovy® arm: 3 patients (0.9%), Truvada® arm: 6 patients (1.8%), which is consistent with Odefsey® and Eviplera®, respectively).
- One Phase I cross-over bioequivalence study evaluating the bioequivalence of Odefsey® to rilpivirine from the single-agent rilpivirine product (Edurant®) and to the emtricitabine and tenofovir alafenamide components of Genvoya® in healthy volunteers (Study 1159).
- 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 Odefsey® and Genvoya® were bioequivalent, consideration of the Genvoya® versus Stribild® trials and Genvoya® cohort study was justified. Evidence was not presented to support the bioequivalence of the emtricitabine and tenofovir

disoproxil fumarate components of Eviplera® and Stribild® to support the relevance of the trials to the nominated comparator of Eviplera®.

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

Trial ID	Protocol title/ Publication title	Publication citation
Key randomised controlled trial (Phase III)		
Study 1089 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. *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.*	22 September 2015 (revised 13 November 2015) *Lancet HIV 2016; published online 14 March 2016 http://dx.doi.org/10.1016/S2352-3018(16)00024-2*
Bioequivalence study (Phase I)		
Study 1159 GS-US-366-1159	A Phase 1, Randomised, Open-Label, Single-Dose, Three-Way, Six-Sequence, Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine, Rilpivirine and Tenofovir Alafenamide from a Fixed Dose Combination of Emtricitabine/Rilpivirine/Tenofovir Alafenamide Relative to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination and Rilpivirine. Final Clinical Study Report. Zack J, Chuck S, Chu H, *et al.* Bioequivalence of the rilpivirine/emtricitabine/tenofovir alafenamide single-tablet regimen.	28 April 2015 *J Bioequiv Availab* 2016; 8(2): 49-54.
Supplementary randomised controlled trials (Phase III)		
Study 104 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 Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment- Naive Adults. Interim Week 96 Clinical Study Report. 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. *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.*	6 October 2014 2 October 2015 *Lancet* 2015; 385 (9987): 2606-2615. *J Acquir Immune Defic Syndr 2016 [Epub ahead of print]*
Study 111 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. 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.	13 October 2014 2 October 2015 *Lancet* 2015; 385 (9987): 2606-2615.

Trial ID	Protocol title/ Publication title	Publication citation
	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.	
Supplementary open-label cohort study		
Study 112 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: Adapted from Table B-5, pp39-40 of the submission and folder entitled 'references'. *Poster presentations were not included.*

6.7 The key features of the randomised trials and non-randomised study are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design / duration	Risk of bias	Patient population	Intervention	Key outcome(s)
Key randomised controlled trial (Phase III)						
Study 1089	668	R, DB, MC 48 wks (96 wks ongoing)	*Low*	HIV-1 positive, treatment-experienced, virologically supressed on Truvada®-based regimens	Descovy® + 3rd agent vs Truvada® + 3rd agent	% with HIV RNA <50 copies/mL at Week 48
Rilpivirine subgroup	9		*Unclear*	Third agent: rilpivirine	Descovy® + rilpivirine vs Truvada® + rilpivirine	
Efavirenz subgroup	14		*Unclear*	Third agent: efavirenz	Descovy® + efavirenz vs Truvada® + efavirenz	
Nevirapine subgroup	140		*Unclear*	Third agent: nevirapine	Descovy® + nevirapine vs Truvada® + nevirapine	
Bioequivalence study (Phase I)						
Study 1159	96	R, OL, CO Single dose, 14 days wash-out period	*Low*	Healthy volunteers, 18-45 years	Odefsey® versus rilpivirine (Edurant®) or Genvoya® (6 treatment sequences)	PK parameters
Supplementary randomised controlled trials (Phase III)						
Study 104	872	R, DB, MC 48 and 96 wks (144 wks ongoing)	*Low*	HIV-1 positive, treatment naïve	Genvoya® versus Stribild®	% with HIV RNA <50 copies/mL at Week 48
Study 111	872	R, DB, MC 48 and 96 wks (144 wks ongoing)	*Low*	HIV-1 positive, treatment naïve	Genvoya® versus Stribild®	% with HIV RNA <50 copies/mL at Week 48
Supplementary open-label cohort study						
Study 112	252	OL, MC, cohort 24 wks, 96 wks data from poster	*NA*	HIV positive, eGFR 30-69 mL/min, virologically suppressed treatment-experienced and treatment-naïve	Genvoya®	Change from baseline at Week 24 in eGFR[a] % with HIV RNA <50 copies/mL at Week 24

Source: constructed during the evaluation

Abbreviations: DB = double-blind; CO = cross-over; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; MC = multi-centre; NA = not applicable; OL = open-label; PK = pharmacokinetic; R = randomised; RNA = ribonucleic acid

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

Comparative effectiveness

6.8 **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)[a]
	Descovy® + 3rd agent	Truvada® + 3rd agent	
Overall population	314/333 (94.3)	307/330 (93.0)	1.3 (-2.5, 5.1)
Ad hoc subgroup analysis			Difference in % (95% CI)[b]
Rilpivirine	3/3 (100)	5/6 (83.3)	16.7 (-13.2, 46.5)
Efavirenz	8/8 (100)	5/6 (83.3)	16.7 (-13.2, 46.5)
Nevirapine	72/74 (97.3)	65/66 (98.5)	-1.2 (-5.9, 3.5)

Source: Tables B-20, p64 and B-27, p70 of the submission; *Study 1089 CSR req7544 Table 1.5, 1.7 and 1.9*

Abbreviations: HIV = human immunodeficiency virus; RD = risk difference; RNA = ribonucleic acid

[a] 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.

[b] Difference in percentages of virologic success between treatment groups and its 95% CI were calculated based on the normal approximation.

Note: Descovy® contains emtricitabine 200mg/ tenofovir alafenamide 25mg or 10mg. Truvada® contains emtricitabine 200mg/ tenofovir disoproxil fumarate 300mg. 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.

6.9 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%.

6.10 The submission stated that the virologic success rates were high and similar between groups across all third agents, including the rilpivirine subgroup and all the NNRTI subgroups, demonstrating that rilpivirine plus emtricitabine plus tenofovir alafenamide yielded high clinical efficacy in this patient population. The submission also stated that the 95% CIs of the subgroups were wide due to the small patient numbers. The submission also noted that no cases of virologic failure were recorded in rilpivirine plus emtricitabine plus tenofovir alafenamide subgroup [of three patients]. Overall, the clinical data from Study 1089 were largely non-informative to support the PBS-listing of Odefsey®, given the very small patients numbers on the combination of rilpivirine plus emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate. The subgroup analysis of patients on rilpivirine as the third agent was highly likely to be underpowered for any comparison.

6.11 For cross-over single-dose bioequivalence study (Study 1159), the GLSM ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for rilpivirine, emtricitabine, and tenofovir alafenamide were contained within the pre-specified bioequivalence boundary criteria of 80% to 125%. The submission concluded that: the rilpivirine component of Odefsey® is bioequivalent to Edurant® (rilpivirine 25mg); and the emtricitabine and tenofovir alafenamide components of Odefsey® are bioequivalent to Genvoya®. The results supported these conclusions.

6.12 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

6.13 The submission argued that it was reasonable to consider that overall safety results from Study 1089 were broadly generalisable to those using rilpivirine as the third agent (Descovy® arm: 3 patients, Truvada® arm: 6 patients), more consistent with the comparison between Odefsey® and Eviplera®. The submission noted none of these [nine] patients died or discontinued study drug due to adverse event.

6.14 The safety data from the entire trial population (Study 1089), as well as the supplementary trials using Genvoya® (Studies 104 and 111), appeared broadly informative given that two of the components of Odefsey® (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.

6.15 The submission presented very limited safety data on rilpivirine.

6.16 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.

6.17 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.

6.18 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 noted 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.

6.19 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.

6.20 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 Odefsey® versus Eviplera®.

6.21 The submission did not provide evidence of comparative safety versus non-tenofovir disoproxil fumarate containing highly active antiretroviral therapies.

6.22 There were limited long-term safety data of ARTs regimens containing tenofovir alafenamide.

Clinical claim

6.23 The submission described Odefsey® as non-inferior in terms of comparative efficacy and non-inferior in terms of comparative safety versus Eviplera®, with a favourable safety profile.

6.24 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.25 The PBAC considered that the claim of a “favourable” safety profile 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 Odefsey® 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

6.26 The submission presented a cost-minimisation analysis.

6.27 The submission stated that one Odefsey® tablet (rilpivirine 25mg + emtricitabine 200mg + tenofovir alafenamide 25mg) and one Eviplera® tablet (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + rilpivirine 25 mg) once daily are equi-effective. The PBAC accepted these equi-effective doses.

6.28 The basis for the equi-effective doses were: the emtricitabine and tenofovir alafenamide components of Odefsey® are bioequivalent to those components obtained from Genvoya® and the rilpivirine component of Odefsey® is bioequivalent to rilpivirine as Edurant®; and the doses of Eviplera® and Odefsey® were consistent with dosing regimens outlined in their respective Product Information documents.

6.29 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 (Highly Specialised Drug Program - Community Access)

	Unit	AEMP/unit (April 2016)	Wholesale mark-up	PtP/unit	Max Qty	PtP/ Max Qty	Pharmacy mark-up	Dispensing fee	DPMQ
Odefsey®	1 box (30 tablets)	$998.43	-	$998.43	2	$1,996.86	$40.00	$6.93	$2,043.79
Eviplera®	1 box (30 tablets)	$998.43	-	$998.43	2	$1,996.86	$40.00	$6.93	$2,043.79

Source: Adapted from Table D-1, p 133 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: $12,433.05

6.30 The drug cost per patient per year of both Odefsey® and Eviplera® was calculated as $12,433.05. Treatment with ARTs, including Odefsey® and Eviplera®, 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 $2,043.79 per 60 tablets.

Estimated PBS usage & financial implications

This submission was not considered by DUSC. The submission used a market share approach, assuming pack-for-pack substitution of Odefsey® for Eviplera® from its projected market. The submission assumed that there was no additional growth of the Eviplera® market due to the PBS-listing of Odefsey®.

Table 5: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of Eviplera® services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odefsey® market share	50%	75%	85%	85%	85%
Number of Odefsey® services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Odefsey® packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost-offset from Eviplera®	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$0	$0	$0	$0	$0
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$0**	**$0**	**$0**	**$0**	**$0**

Source: Tables E-3 to E-4, pp139-141 of the submission

Note: An apparent arithmetic error was amended during the evaluation (DPMQ of $2,016.63 instead of $2,043.79 was applied for both Odefsey® and Eviplera®). The submission did not round the numbers of packs/services to the closest whole number.

The redacted table shows that, at Year 5, the estimated number of Evilplera and Descovy services was 10,000 – 50,000.

6.31 The submission estimated that the listing of Odefsey® would be cost neutral for the government due to the identical price and pack-for-pack substitution of Odefsey® for Eviplera®.

6.32 The key areas of uncertainties in the estimates include:

- The submission failed to consider uptake from products apart from Eviplera®, and therefore may have underestimated the potential market for Odefsey®.
- There were concerns that the projected Eviplera® market was an overestimate based on the comparison of predicted data versus available actual data.

Quality Use of Medicines

6.33 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*

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

6.35 The submission claimed that Odefsey® significantly improved compliance, significantly improved efficacy and significantly reduced toxicity for some patients compared to the nominated alternative multi-tablet regimens.

6.36 The submission did not make clear claims versus other single-tablet regimens (including the nominated comparator of Eviplera®), which were potential alternative therapies. The PBAC noted it had previously considered other combination products as alternative therapies when providing advice under subsection 101(4AC) of the Act (PBAC Public Summary for Vytorin® November 2014).

6.37 The submission claimed that the safety benefits of tenofovir alafenamide over tenofovir disoproxil fumarate were due to the lower systemic tenofovir exposure associated with tenofovir alafenamide (stated as 90% less than tenofovir disoproxil fumarate). The PBAC agreed with the ESC that 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 (including regimens containing a Kivexa® backbone, which was nominated as one of the alternative therapies).

6.38 The submission also identified a literature review and meta-analysis by Clay et al (2015) comparing single-tablet regimens versus multi-tablet regimens in the treatment of HIV infection as key evidence to support its claims of improved benefit in terms of efficacy, safety, and compliance. Based on the results from Clay et al (2015), the submission claimed that patients on single-tablet regimens had significantly better viral load suppression, fewer Grade 3 and 4 laboratory abnormalities, better adherence, and reduced health resource utilisation and costs compared to those on multi-tablet regimens. The PBAC agreed with the ESC that none of the multi-tablet regimens were consistent with the ART regimen of Odefsey®. The extent of use of multi-tablet regimens with Kivexa® and Truvada® backbones (the nominated alternative comparator) was unclear. There were a number of concerns relating to the methodology and the results of Clay et al (2015), which included the exclusion of a large number of studies on the basis of the lack of 'analysable' data,

the lack of consideration of other differences between the treatment arms apart from the numbers of tablets (e.g. differences in the ARTs in the regimens), the accuracy of the data extraction by the authors, and the pooling of non-comparable adherence outcomes. The submission appeared to overstate the economic findings of Clay at el (2015), as the authors concluded that the analyses discovered potentially reduced treatment and healthcare resource use and costs (of which there were concerns that the results were not systematically reviewed). Overall, Clay et al (2015) did not provide adequate evidence to support the submission's claim that that Odefsey® is associated with a significant improvement in toxicity, compliance and efficacy for some patients versus multi-tablet regimens with Kivexa® or Truvada® backbones.

6.39 The submission specifically identified a subgroup of patients for whom Odefsey® may offer compliance advantages: patients with renal impairment (eGFR <50mL/min) and with HLA-B*5701 genotype, for whom the submission claimed that a complex regimen of individual ARTs that either dose-adjusted or have dose interval adjustment is required. The submission did not estimate the size of this subset of patients, but had noted that 5% of exposed patients (or 8% of Caucasians) have the HLA-B*5701 allele. However, Genvoya®, which is administered as one tablet daily, may be an appropriate therapy for this subset of patients.

6.40 Overall, the PBAC considered there remained uncertainty that changes in surrogate outcomes of bone and renal safety at Week 96 are sufficient to support the claimed significant reduction in toxicity in some patients over a lifetime. The PBAC also considered there was no evidence to support the claim of significantly improved compliance or efficacy and that single tablet fixed dose combination regimens are also equally legimate choices as alternative therapies.

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 and rilpivirine 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 Odefsey®, Eviplera® 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 Odefsey® 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 Odefsey® (rilpivirine 25mg + emtricitabine 200mg + tenofovir alafenamide 25mg tablet) is non inferior Eviplera® (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + rilpivirine 25 mg tablet) in terms of

effectiveness and safety. The equi-effective doses are one tablet of Odefsey is equivalent to one tablet of Eviplera.

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, albeit the number of patients in the rilpivirine subgroup was small.

7.5 The PBAC considered the sponsor's request to have the restrictions for recently listed single tablet regimen antiretroviral treatments also apply to a listing of Odefsey® to be appropriate.

7.6 The PBAC formed the view that the Early Supply Rule should apply to Odefsey®, as recommended for all HIV treatments at the November 2015 meeting.

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

7.7 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 6.36-6.40, 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.