

## 5.02 BICTEGRAVIR + EMTRICITABINE + TENOFOVIR ALAFENAMIDE FIXED DOSE COMBINATION, Tablet containing tenofovir alafenamide 25 mg with emtricitabine 200 mg and bicitegravir 50 mg, Biktarvy®, Gilead Sciences Pty Ltd

### 1 Purpose of Application

- 1.1 The submission requested an Authority Required (Streamlined) Section 100 listing for a fixed dose combination (FDC) tablet containing bicitegravir with emtricitabine and tenofovir alafenamide, referred to as BFTAF herein, for the treatment of treatment-naïve and virologically suppressed human immunodeficiency virus (HIV-1) infected patients. BFTAF has not been considered by the PBAC previously.
- 1.2 The submission requested listing for BFTAF on a cost minimisation basis against the primary comparator DESCovy® (emtricitabine + tenofovir alafenamide FDC) plus dolutegravir, and two secondary comparators, GENVOYA® (elvitegravir, emtricitabine + tenofovir alafenamide FDC) and ODEFSEY® (emtricitabine, rilpivirine + tenofovir alafenamide FDC), that is, tenofovir alafenamide (TAF)-based FDCs.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Adults with HIV-1 infection
Intervention	Fixed-dose combination (FDC) tablet of bicitegravir 50mg + emtricitabine 200mg + tenofovir alafenamide 25mg
Comparator	<p><u>Primary:</u></p> <ul style="list-style-type: none"> <li>DESCovy® (FDC of emtricitabine 200mg &amp; tenofovir alafenamide 10/25mg) + dolutegravir 50mg</li> </ul> <p><u>Secondary:</u></p> <ul style="list-style-type: none"> <li>GENVOYA® (FDC of tenofovir alafenamide 10 mg + emtricitabine 200 mg + elvitegravir 150 mg + cobicistat 150 mg);</li> <li>ODEFSEY® (FDC of emtricitabine 200 mg + rilpivirine 25 mg + tenofovir alafenamide 25 mg)</li> </ul> <p>These are not the only relevant alternative therapies</p>
Outcomes	Virological suppression (patients with plasma HIV RNA <50 copies per mL using the FDA snapshot algorithm)
Clinical claim	The FDC of bicitegravir 50mg + emtricitabine 200mg + tenofovir alafenamide 25mg (BFTAF) is non-inferior in terms of efficacy and safety, compared to emtricitabine + tenofovir alafenamide (FTAF)-based regimens

BFTAF = bicitegravir, emtricitabine and tenofovir alafenamide; FDA = Food and Drug Administration; FDC = Fixed-dose combination; FTAF = emtricitabine and tenofovir alafenamide; HIV = human immunodeficiency virus; mg = milligram; RNA = ribonucleic acid  
 Source: Table 1.2, p14 of the submission.

## 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BICTEGRAVIR+EMTRICITABINE+TENOFIVIR ALAFENAMIDE 50MG+200MG+25MG, TABLET.	2	5	\$2,016.85	Biktary® Gilead Sciences Pty Ltd
<b>Category/Program:</b>	Section 100			
<b>Episodicity:</b>	Daily, continuous treatment			
<b>Condition:</b>	HIV infection			
<b>PBS Indication:</b>	HIV infection			
<b>Treatment phase:</b>	Initial			
<b>Restriction:</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>Treatment phase:</b>	Continuing			
<b>Restriction</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			

2.1 No special pricing arrangement was proposed.

*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, no TGA documents were available (except a draft PI). The submission indicated that BFTAF is scheduled to be considered at the ACPM on 1 June 2018 with the Clinical Evaluator's Report expected on 31 March 2018 and the Delegate's Overview on 1 May 2018.

3.2 The therapeutic relativity sheets (1 January 2018) indicate that all triple-therapy FDCs (with the exception of TRIZIVIR®; abacavir + lamivudine + zidovudine) listed for the treatment of HIV, i.e. ATRIPLA® (emtricitabine + tenofovir disoproxil fumarate + efavirenz), TRIUMEQ® (dolutegravir + abacavir + lamivudine), STRIBILD® (cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate), EVIPLERA® (tenofovir disoproxil fumarate + emtricitabine + rilpivirine), GENVOYA® and ODEFSEY® are considered non-inferior given their history of being listed on a cost-minimisation basis. Additionally, DESCOVY® was recommended on a cost-minimisation basis with TRUVADA® (tenofovir disoproxil fumarate + emtricitabine).

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

## **4 Population and disease**

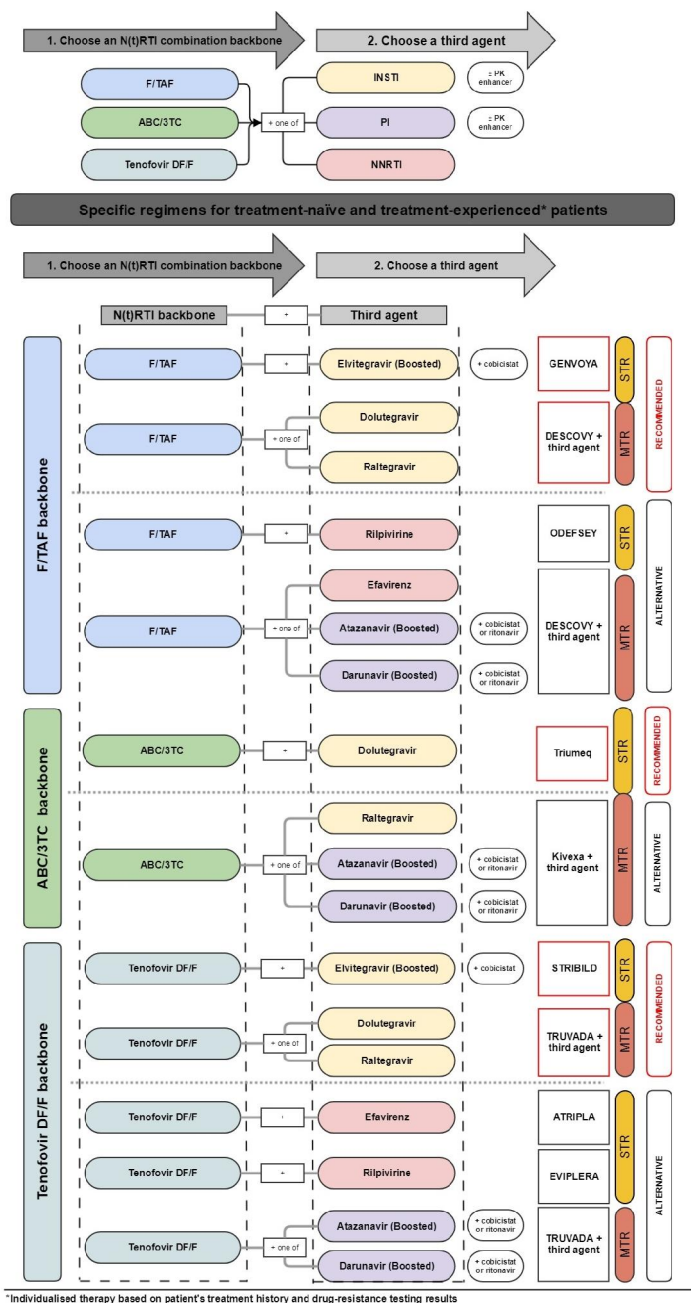
- 4.1 Human immunodeficiency virus (HIV) infection is characterised by a dramatic reduction in the number of CD4+ T-cells causing damage to, and deterioration of, immune function, and subsequent increase in risk of opportunistic infections and malignancies resulting in debilitating conditions, reduced quality of life and death. According to the Kirby Institute (2016), it was estimated there were 25,313 people living with HIV in Australia in 2015. Of these, an estimated 22,694 were diagnosed, 21,560 were retained in care, 19,051 were receiving antiretroviral therapy (ART), and 17,544 had achieved viral suppression. The overall prevalence of HIV in Australia was estimated to be 0.13%.
- 4.2 The listing of BFTAF would only alter the current management algorithm by making another emtricitabine/tenofovir alafenamide (FTAF) combination available for treatment-naïve and treatment-experienced patients.

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

## **5 Comparator**

- 5.1 The submission nominated DESCOVY® plus dolutegravir as the main comparator, and nominated GENVOYA® and ODEFSEY® as supplementary comparators. The basis of this nomination was that they were all emtricitabine and tenofovir alafenamide (FTAF) based regimens, and were therefore the regimens most likely to be replaced.
- 5.2 The comparators nominated by the submission were appropriate, however all therapies currently PBS-listed for the treatment of HIV would represent potential alternative therapies. Alternative therapies to BFTAF are presented in Table 9 and Figure 1. For clarity and concision, only PBS-listed fixed dose combination (FDC) treatments are presented. However, as the currently PBS-listed therapies for HIV can be used in various combinations, this list of alternative therapies is by no means exhaustive.
- 5.3 The submission nominated TAF-based fixed dose combination therapies only as the comparators. Each of these TAF-based FDCs (DESCOVY® July 2016 PBAC Meeting, GENVOYA® November 2015 PBAC Meeting, ODEFSEY® July 2016 PBAC Meeting) have previously been accepted by the PBAC as being non-inferior to their respective tenofovir disoproxil fumarate (TDF)-based FDCs (TRUVADA®, STRIBILD®, EVIPLERA®). It was also noted that the comparator arm of Trial 1878 (presented as the evidence base of the submission for virologically suppressed/treatment-experienced patients) included patients treated with ritonavir boosted or cobicistat boosted atazanavir or darunavir, with either TRUVADA® or KIVEXA® (abacavir/lamivudine FDC; ABC/3TC). This further suggests that TDF and ABC/3TC-containing treatments may also be reasonable comparators.

Figure 1: Current HIV management algorithm



Source: Figure 1.4, p30 of the submission.

3TC = lamivudine, ABC = abacavir, F = emtricitabine, INSTI = integrase strand transfer inhibitor, MTR = multiple tablet regimen, N(t)RTI = nucleotide reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK enhancer = pharmacokinetic enhancer, STR = single tablet regimen, TAF = tenofovir alafenamide fumarate, Tenofovir DF = tenofovir disoproxil fumarate

- 5.4 For the requested population, a number of other combination therapies are less costly than GENVOYA® and ODEFSEY® (and therefore the requested price for BFTAF).
- 5.5 The Pre-Sub-Committee Response (PSCR) and Pre-PBAC Response disagreed that additional comparators outside those nominated in the submission were relevant,

citing utilisation data to suggest that listing of BFTAF would not significantly alter the usage rates across the ‘backbone’ groups. The PSCR and Pre-PBAC Response argued that therapies other than the nominated comparators are not viable comparators because they would not be replaced by BFTAF in clinical practice. The PSCR further inferred that providing patients with a single treatment regimen was an important consideration in guiding treatment selection with consequences for long term adherence.

- 5.6 The ESC considered the nominated TAF-based FDC therapies were appropriate comparators. However, the ESC considered that all triple-therapy FDCs for the treatment of HIV that are included in the therapeutic relativity sheets (1 January 2018) are considered to be non-inferior to each other in terms of both safety and efficacy and thus have a history of being listed on a cost-minimisation basis. The ESC also considered that arguments for a single treatment regimen over a multiple treatment regimen based on long term adherence were not sufficient to change either of these conclusions of non-inferiority, recalling that PBAC had only accepted such a link would be realised with more substantial reductions in “pill burden” than would be likely in this context. The ESC therefore advised that the least expensive triple-therapy FDC for the treatment of HIV would be the most relevant alternative therapy for the purposes of Section 101 (3B) of the *National Health Act 1953*.
- 5.7 The submission presented no data to establish superiority (and cites PBS-accepted therapeutic relativities of TDF-based and ABC/3TC-based FDCs), thus there is no justification for the price of BFTAF to be higher than the least expensive of these alternative therapies. In its July 2016 considerations of ODEFSEY® and DESCOVY®, the PBAC accepted TDF-based regimens (EVIPLERA® and TRUVADA®, respectively) as the only comparator. In its July 2015 consideration of GENVOYA®, the PBAC accepted STRIBILD® as the most appropriate comparator, but agreed with ESC that GENVOYA® might also displace other emtricitabine/tenofovir disoproxil fumarate-containing single tablet and multi-tablet highly active antiretroviral therapies as well as TRIUMEQ® for adolescents and patients with renal impairment.
- 5.8 The PBAC considered the submission’s nominated comparators of DESCOVY® plus dolutegravir (main comparator), and GENVOYA® and ODEFSEY® (supplementary comparators) to be appropriate. However the PBAC agreed with the ESC that all triple-therapy FDCs for the treatment of HIV could be considered alternative therapies.

*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 direct randomised trials:

- GS-US-380-1490 (Trial 1490; n=600), comparison of BFTAF and DESCOVY® plus dolutegravir in treatment-naïve patients
- GS-US-380-1878 (Trial 1878; n=520), comparison of patients switching to BFTAF and those who stayed on their baseline regimen (SBR) consisting of either cobicistat or ritonavir boosted atazanavir or darunavir plus either TRUVADA® or KIVEXA® in virologically suppressed (treatment-experienced) patients.

6.4 The submission also identified two supplementary trials (included only by the submission in the “Extended assessment of comparative harms”):

- GS-US-380-1489 (Trial 1489; n=629) comparison of BFTAF to TRIUMEQ® in treatment-naïve patients
- GS-US-380-1844 (Trial 1844, n=563) comparison of patients switching to BFTAF and those who stayed on a regimen of KIVEXA® + dolutegravir or TRIUMEQ® in virologically suppressed (treatment-experienced) patients.

6.5 The exclusion of Trials 1489 and 1844 from the clinical evaluation presented in the submission was based on the absence of an emtricitabine/tenofovir alafenamide comparator arm, which was inconsistent with the inclusion of Trial 1878. These other treatment regimens represent alternative therapies and their exclusion may not be appropriate. The Pre-PBAC Response argued that the comparison of BFTAF to ABC/3TC-based regimens in Trials 1489 and 1844 was not relevant in the context of the Australian treatment algorithm.

6.6 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Key trials</b>		
Study 1490	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al., Coformulated bicitegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial.	May 2017  Lancet. 2017; pii S0140-6736(17)32340-2437
Study 1878	A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults	May 2017
<b>Supplementary trials</b>		
Study 1489	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczar D, Tebas P, et al., Bicitegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial.	May 2017.  Lancet. 2017;pii: S0140-6736(17)32299-7.
Study 1844	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of TRIUMEQ® to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed	May 2017

Source: Table 2.4, p45 of the submission.

6.7 The key features of the direct randomised trials included in the submission are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>BFTAF versus DESCOVY® plus dolutegravir</b>					
Trial 1490	600	R, DB At least 144 weeks	Low	Treatment Naïve	Proportion of patients with plasma HIV RNA <50 copies per mL using the FDA snapshot algorithm.
<b>BFTAF versus staying on baseline regimen (SBR: cobicistat or ritonavir boosted atazanavir or darunavir plus either TRUVADA® or KIVEXA®)</b>					
Trial 1878	520	R, OL At least 48 weeks	Low	Virologically suppressed	Proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm
<b>BFTAF versus TRIUMEQ® or KIVEXA® plus dolutegravir</b>					
Trial 1489	629	R, DB At least 48 weeks	Low	Treatment Naïve	Proportion of patients with plasma HIV RNA <50 copies per mL using the FDA snapshot algorithm.
Trial 1844	563	R, DB, At least 48 weeks	Low	Virologically suppressed	Proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm

DB=double blind; OL=open label; R=randomised.

Source: pp47-66 of the submission, Table 2, p11 of 'TGA Dossier Section 2.5 (Clinical Overview)'

6.8 The ESC considered there was a moderate risk of bias in the evidence reported for the endpoints from Study 1878 as it was an open-label study.

### Comparative effectiveness

6.9 For treatment-naïve patients, Table 4 presents the primary endpoint of proportion of patients with <50 copies/mL of HIV-1 RNA (as per the FDA snapshot algorithm) from Trial 1490. The proportion of patients with <50 copies were similar between the BFTAF and DESCOVY® + dolutegravir treatment groups, with a non-significant difference of -3.5%. The submission considered that because the lower bound of the 95% CI (-7.9%) was greater than the pre-specified -12% margin, BFTAF was considered to be non-inferior to DESCOVY® + dolutegravir. This was reasonable.

**Table 4: Results of Trial 1490, primary endpoint**

Virological outcome at 48 weeks	BFTAF N=320 n (%)	DESCOVY® + Dolutegravir N=325 n (%)
HIV-1 RNA <50 copies/mL	286 (89.4%)	302 (92.9%)
Difference in percentages (95% CI), p-value	-3.5% (-7.9% to 1.0%), p=0.12	
HIV-1 RNA ≥50 copies/mL	14 (4.4%)	4 (1.2%)
HIV-1 RNA ≥50 copies/mL in Week 48 Window	3 (0.9%)	1 (0.3%)
Discontinued study drug due to lack of efficacy	0	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL	11 (3.4%)	3 (0.9%)
No virological data in Week 48 window	20 (6.3%)	19 (5.8%)
Discontinued study drug due to AE/death	3 (0.9%)	3 (0.9%)
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/mL	11 (3.4%)	14 (4.3%)
Missing data during window but on study drug	6 (1.9%)	2 (0.6%)

AE = adverse event; CI = confidence interval; HIV = human immunodeficiency virus; mL = millilitre; RNA = ribonucleic acid;  
Source: Table 2.14, p68 of the submission.

6.10 Trial 1489 (n=629), excluded from the submission’s clinical evaluation, provided a comparison of BFTAF to TRIUMEQ® in treatment-naïve patients. The trial was randomised and double-blind and considered to be at a low risk of bias. Patient characteristics were balanced between treatment arms. The primary outcome was proportion of subjects with HIV-1 RNA <50 copies/mL using the US FDA-defined snapshot algorithm and a non-inferiority margin of -12% was specified. 92.4% of the BFTAF group had <50 copies/mL at Week 48 compared to 93.3% in the TRIUMEQ® group, with a non-significant difference of -0.9% (95% CI: -5.1%, 3.2%). The results indicated non-inferior efficacy.

6.11 For virologically suppressed patients, Table 5 presents the primary endpoint of proportion of patients with ≥50 copies/mL of HIV-1 RNA (as per the FDA snapshot algorithm) from Trial 1878. The proportions were similar in each treatment group (-0.0% difference). The submission considered that because the upper bound of the 2 sided 95% CI of the difference between the treatment groups was less than the pre-specified 4% margin, switching to BFTAF was determined to be non-inferior to maintaining baseline regimens. This was reasonable.

**Table 5: Results of Trial 1878, primary endpoint**

<b>Virological outcome at 48 weeks</b>	<b>BFTAF; N=290 n (%)</b>	<b>SBR; N=287 n (%)</b>
HIV-1 RNA <50 copies/mL	267 (92.1%)	255 (88.9%)
Difference in percentages (95% CI) p-value	3.2% (-1.6% to 8.2%) p=0.22	
HIV-1 RNA ≥50 copies/mL	5 (1.7%)	5 (1.7%)
Difference in percentages (95% CI)	-0.0% (-2.5% to 2.5%) p=1.00	
HIV-1 RNA ≥50 copies/mL in Week 48 Window	2 (0.7%)	2 (0.7%)
Discontinued study drug due to lack of efficacy	1 (0.3%)	0
Discontinued study drug due to AE/death and last available HIV-1 RNA ≥50 copies/mL	0	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL	2 (0.7%)	3 (1.0%)
No virological data in Week 48 window	18 (6.2%)	27 (9.4%)
Discontinued study drug due to AE/death and last available HIV-1 RNA <50 copies/mL	3 (1.0%)	2 (0.7%)
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/mL*	10 (3.4%)	19 (6.6%)
Missing data during window but on study drug	5 (1.7%)	6 (2.1%)

AE = adverse event; BFTAF = bicitegravir, emtricitabine, tenofovir alafenamide; CI = confidence interval; mL = millilitre; RNA = ribonucleic acid; SBR = stayed on baseline regimen

Source: Table 2.17, p72 of the submission.

- 6.12 Trial 1844 (n=563), excluded from the submission's clinical evaluation, provided a comparison of patients switching to BFTAF and those who stayed on a regimen of KIVEXA® + dolutegravir or TRIUMEQ® in virologically suppressed (treatment-experienced) patients. The trial was randomised and double-blind and considered to be at a low risk of bias. Patient characteristics were balanced between treatment arms. The primary outcome was the proportion of subjects with HIV-1 RNA ≥50 copies/mL (using the US FDA-defined snapshot algorithm) and a non-inferiority margin of 4% was specified. 1.1% of the BFTAF group had at least 50 copies of HIV RNA/ mL compared to 0.4% in the TRIUMEQ® group. The results indicate non-inferiority between the two treatments.
- 6.13 The ESC considered the use of HIV RNA outcomes as defined using the FDA snapshot algorithm was appropriate, noting that both GENVOYA® and DESCOVY® submissions were based on HIV RNA assessments using the FDA snapshot algorithm (DESCOVY® July 2016 PSD; GENVOYA® November 2015 PSD).
- 6.14 Overall, the ESC considered that a claim of non-inferiority in terms of effectiveness of BFTAF compared with the following regimens was supported by the trial evidence:
- DESCOVY® + dolutegravir in treatment-naïve patients
  - staying on baseline regimen (with a TRUVADA®- or KIVEXA®- backbone) in virologically suppressed (treatment-experienced) patients
  - TRIUMEQ® in treatment-naïve patients
  - staying on baseline KIVEXA® + dolutegravir or TRIUMEQ® in virologically suppressed patients.

## Comparative harms

6.15 Table 6 presents a summary of adverse events in Trial 1490.

**Table 6: Summary of adverse events in Trial 1490**

Type of Adverse Event	BFTAF; N=320	FTAF + DTG; N=325	RD (95% CI)
Any treatment-emergent AE	264 (82.5%)	272 (83.7%)	-0.01 (-0.07, 0.05)
Any Grade 2, 3, or 4 treatment-emergent AE	141 (44.1%)	132 (40.6%)	0.03 (-0.04, 0.11)
Any Grade 3 or 4 treatment-emergent AE	33 (10.3%)	25 (7.7%)	0.03 (-0.02, 0.07)
Any treatment-emergent study drug-related AE	57 (17.8%)	83 (25.5%)	<b>-0.08 (-0.14, -0.01)</b>
Any Grade 2, 3, or 4 treatment-emergent study drug-related AE	14 (4.4%)	5 (1.5%)	0.03 (0, 0.05)
Any Grade 3 or 4 treatment-emergent study drug-related AE	3 (0.9%)	0	0.01 (0, 0.02)
Any treatment-emergent serious AE	39 (12.2%)	23 (7.1%)	<b>0.05 (0.01, 0.1)</b>
Any treatment-emergent study drug-related serious AE	2 (0.6%)	0	0.01 (0, 0.01)
Any treatment-emergent adverse event leading to premature study drug discontinuation	5 (1.6%)	1 (0.3%)	0.01 (0, 0.03)
Treatment-emergent death	1 (0.3%)	2 (0.6%)	0 (-0.01, 0.01)

AE = adverse event; BFTAF = bictegravir, emtricitabine and tenofovir alafenamide; CI = confidence interval; DTG = dolutegravir; FTAF = emtricitabine & tenofovir alafenamide; RD = risk difference;

Note: Risk differences calculated during the evaluation. Bold text signifies statistically significant differences.

Table 2.21, p 75 and 76 of the submission.

6.16 There was a higher proportion of patients with any Grade 2, 3 or 4 treatment-emergent study drug related adverse events among those treated with BFTAF (4.4%) compared with DESCOVY® + dolutegravir (1.5%), and any treatment-emergent serious AEs among those treated with BFTAF (12.2%) compared with DESCOVY® + dolutegravir (7.1%). Conversely, there was a higher rate of any treatment-emergent study drug related AE among those treated with DESCOVY® + dolutegravir (25.5%) compared with BFTAF (17.8%). Overall the ESC considered that the safety profile was comparable in treatment-naïve patients.

6.17 Table 7 present the summary of adverse events in Trial 1878.

**Table 7: Summary of adverse events in Trial 1878**

Type of Adverse Event	BFTAF; N=290	SBR; N=287	RD (95%CI)
Any treatment-emergent AE	233 (80.3%)	226 (78.7%)	0.02 (-0.05, 0.08)
Any grade 2, 3, or 4 treatment-emergent AE	125 (43.1%)	93 (32.4%)	<b>0.11 (0.03, 0.19)</b>
Any grade 3 or 4 treatment-emergent adverse event	13 (4.5%)	18 (6.3%)	-0.02 (-0.05, 0.02)
Any treatment-emergent study drug-related AE	54 (18.6%)	6 (2.1%)	<b>0.17 (0.12, 0.21)</b>
Any grade 2, 3, or 4 treatment-emergent study drug-related AE	15 (5.2%)	1 (0.3%)	<b>0.05 (0.02, 0.07)</b>
Any grade 3 or 4 treatment-emergent study drug-related AE	2 (0.7%)	0	0.01 (0, 0.02)
Any treatment-emergent serious AE	17 (5.9%)	20 (7.0%)	-0.01 (-0.05, 0.03)
Any treatment-emergent study drug-related serious AE	1 (0.3%)	0	0 (0, 0.01)
Any treatment-emergent AE leading to premature discontinuation	2 (0.7%)	1 (0.3%)	0 (-0.01, 0.02)

Table 2.24, p79 of the submission. AE = adverse event; BFTAF = bictegravir, emtricitabine, tenofovir alafenamide; CI = confidence interval; RD = risk difference; SBR = stayed on baseline regimen

Note: Risk differences calculated during the evaluation. Bold text signifies statistically significant differences.

6.18 There was a statistically significant higher proportion of patients treated with BFTAF compared with those who stayed on their baseline regimen for:

- any grade 2, 3 or 4 treatment-emergent AE

- any treatment emergent study drug related adverse event
- any grade 2, 3, or 4 treatment-emergent study drug-related AE.

6.19 The submission concluded that BFTAF was safe and well tolerated. Common adverse events were generally consistent with those expected in the subject population and the known safety profiles of the study drugs. Given the mixed nature of the comparator in Trial 1878 it was difficult to assess the comparative safety of BFTAF in virologically suppressed patients, however as there were statistically significant increases in adverse events observed among those treated with BFTAF compared to those staying on baseline treatments, the possibility that BFTAF is inferior in terms of safety cannot be excluded.

### **Clinical claim**

6.20 The submission described BFTAF as non-inferior in terms of effectiveness and safety compared with tenofovir alafenamide regimens DESCOVY® + dolutegravir, GENVOYA®, ODEFSEY®.

6.21 The therapeutic conclusion of non-inferior effectiveness presented in the submission was supported by Trial 1490 for the comparison of BFTAF and DESCOVY® + dolutegravir in treatment-naïve patients given the trial met accepted, pre-specified non-inferiority margins. A claim of non-inferior effectiveness of BFTAF to GENVOYA® and ODEFSEY® was not presented or directly supported by any evidence presented in the submission, but may be surmised on the basis of the current accepted relativities of the treatments. This was further supported by data from Trial 1489 (excluded by the submission), which indicated non-inferiority of BFTAF to TRIUMEQ®.

6.22 Trial 1878 supported a conclusion of non-inferior effectiveness of BFTAF to TRUVADA®- and KIVEXA®- based regimens in virologically suppressed (treatment-experienced) patients, with the trial meeting accepted, pre-specified non-inferiority margins. The results observed in Trial 1878 support the contention that there is no justification for BFTAF to be listed at a higher price compared with abacavir and lamivudine regimens or tenofovir disoproxil fumarate regimens. This was further supported by data from Trial 1844 (excluded by the submission), which indicated non-inferiority of BFTAF to KIVEXA® plus dolutegravir or TRIUMEQ®. The Pre-PBAC Response argued against this comparison, claiming that ABC/3TC-based regimens are not relevant in the context of Australian clinical practice.

6.23 In terms of safety, Trial 1490 showed generally similar adverse events in treatment-naïve patients, but Trial 1878 showed higher proportions of select treatment emergent adverse events in patients treated with BFTAF compared to those staying on regimens with a TRUVADA®- or KIVEXA®- backbone. Given the mixed nature of the comparator in Trial 1878 it was difficult to assess the comparative safety of BFTAF in virologically suppressed patients, however as there were statistically significant increases in adverse events observed among those treated with BFTAF

compared to those staying on baseline treatments, the possibility that BFTAF is inferior in terms of safety cannot be excluded. The ESC considered that the submission's extended assessment of comparative harms generally suggested overall similarity in tolerability across all treatments included in the phase three trial program for BFTAF (Trials 1490, 1878, 1489 and 1844).

- 6.24 The ESC considered that BFTAF can be considered non-inferior not only to DESCOVY® + dolutegravir, GENVOYA® and ODEFSEY®, but also to TRIUMEQ®, TRUVADA®- and KIVEXA®-based regimens.
- 6.25 The PBAC considered that the claim of non-inferior comparative effectiveness to tenofovir alafenamide regimens DESCOVY® + dolutegravir, GENVOYA®, ODEFSEY® was reasonable. The PBAC also considered that BFTAF was non-inferior in comparative effectiveness by extension, to all triple-therapy FDCs for the treatment of HIV that are included in the therapeutic relativity sheets (1 January 2018).
- 6.26 The PBAC considered that the claim of non-inferior comparative safety was reasonable noting that, overall, there were no major safety signals in patients that switched to BFTAF from SBR.

### **Economic analysis**

- 6.27 The submission stated that the equi-effective doses were based on Trial 1490 regimens. These doses were consistent with the draft PI of BFTAF and available dosages of DESCOVY® plus dolutegravir on the PBS.
- 6.28 The submission also stated that given recent PBAC recommendations for FTAF-based regimens were on a cost-minimisation basis, it may be appropriate to describe additional equi-effective doses for BFTAF versus other FTAF regimens (GENVOYA® and ODEFSEY®):
- one tablet of BFTAF (50mg/200mg/25mg) and one tablet of GENVOYA® (10/200/150//150) are equi-effective
  - one tablet of BFTAF (50mg/200mg/25mg) daily and one tablet of ODEFSEY® (200/25/25) are equi-effective.
- 6.29 The equi-effective doses of BFTAF versus GENVOYA® and ODEFSEY® were not supported by any trial evidence, but may be surmised on the basis of the current accepted relativities of the treatments. Other evidence additionally indicated non-inferiority of BFTAF to TRUVADA®- and KIVEXA®- based regimens and TRIUMEQ®.
- 6.30 Table 8 presents the results of the cost-minimisation presented by the submission.

**Table 8: Results of the cost-minimisation analysis**

Description	BFTAF	DESCOVY® + dolutegravir	GENVOYA®	ODEFSEY®
PBS Code	NA	11113X + 10283F	11114Y	11104K
Dose (daily mg)	50/200/25	200/25 + 50	10/200/150/150	200/25/25
Dispensed price, maximum quantity (60 tablets)	\$2,016.85	\$1,500.85 + \$1,378.25 = \$2,879.10	\$2,016.85	\$2,016.85
Drug cost per 30 tablet pack	\$1,008.43	\$1,439.55	\$1,008.43	\$1,008.43
Drug cost per 30 tablet pack (ex-manufacturer)	<b>\$984.85</b>	\$726.85 + \$665.55 = <b>\$1,392.40</b>	<b>\$984.85</b>	<b>\$984.85</b>

mg = milligram; NA = not available; PBS = Pharmaceutical Benefits Scheme  
Source: Table 3.3, p 95 of the submission.

6.31 The ESC considered that the three nominated comparators were not the only relevant alternative therapies. Several other regimens were identified as alternative therapies. These are presented in Table 9.

**Table 9: Potential comparators – fixed dose combinations for the treatment of HIV**

Drug name	Brand name	Qty/pack	Ex-man/pack	Backbone	Non-inferior?
TAF 10mg or 25mg, emtricitabine 200mg Dolutegravir 50mg	*DESCOVY®	30	\$726.85	TAF	Yes (Trial 1490)
	*TIVICAY®	30	\$665.55		
TAF 10mg, emtricitabine 200mg, elvitegravir 150mg & cobicistat 150mg	<b>GENVOYA®</b>	30	\$984.85	TAF	Yes (assumed)
TAF 25mg, emtricitabine 200mg, & rilpivirine 25mg	<b>ODEFSEY®</b>	30	\$984.85	TAF	Yes (assumed)
TDF 300mg & emtricitabine 200mg	*TRUVADA®	30	\$610.55	TDF	Yes (Trial 1878) <sup>a</sup>
TDF 300mg, emtricitabine 200mg, elvitegravir 150mg & cobicistat 150mg	<b>STRIBILD®</b>	30	\$868.55	TDF	Yes (assumed)
TDF 300mg, emtricitabine 200mg, & rilpivirine 25mg	<b>EVIPLERA®</b>	30	\$868.55	TDF	Yes (assumed)
TDF 300mg, emtricitabine 200mg & efavirenz 600mg	<b>ATRIPLA®</b>	30	\$868.55	TDF	Yes (assumed)
Abacavir 600mg & lamivudine 300mg	KIVEXA®	30	\$333.41	ABC/3TC	Yes (Trial 1878) <sup>a</sup>
Abacavir 600mg & lamivudine 300mg Dolutegravir 50mg	*KIVEXA®	30	\$333.41	ABC/3TC	Yes (Trial 1844)
	*TIVICAY®	30	\$665.55		
Abacavir 300mg, lamivudine 150mg & zidovudine 300mg	TRIZIVIR®	60	\$538.14	ABC/3TC	Unclear
Dolutegravir 50mg, abacavir 600mg, lamivudine 300mg	* <b>TRIUMEQ®</b>	30	\$940.70	ABC/3TC	Yes (Trials 1489 & 1844)

*Bolded FDCs are listed for the treatment of HIV in the therapeutic relativity sheets (1 January 2018) and are considered to be non-inferior based on their history of being listed on a cost-minimisation basis.*

\* indicates FDCs for which trial data has been presented.

<sup>a</sup> in combination with cobicistat or ritonavir boosted atazanavir or darunavir

ABC/3TC = abacavir and lamivudine; Ex-man = ex-manufacturer; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Source: PBS website.

6.32 The ESC noted that, with the exception of combinations including DESCOVY® plus dolutegravir and KIVEXA® plus dolutegravir, all alternative FDC triple therapies identified had a lower price than BFTAF. Given that both accepted relativities and trial evidence support a claim of non-inferiority to other combination treatments, the ESC considered that a cost-minimisation based on the lowest priced of these may

be justified, given the absence of sufficient evidence to support a benefit over these existing therapies.

- 6.33 The Pre-PBAC Response argued that the most commonly used FTAF-based regimens are the only appropriate comparators, and therefore cost-minimisation against alternative regimens would be unjustified and inappropriate. The Pre-PBAC Response also reiterated that the proposed price for BFTAF is equivalent to the price of the lowest cost comparators GENVOYA® and ODEFSEY® and significantly less than the price of DESCOVY® + dolutegravir, which the submission claims is the regimen most likely to be replaced in clinical practice.

**Drug cost/patient/year**

- 6.34 \$12,101.10, based on a DPMQ of \$2,016.85 (ex-manufacturer price of \$984.85 for 30 days of treatment (30 tablets)) and assuming 6 scripts per year.

**Estimated PBS usage & financial implications**

- 6.35 This submission was not considered by DUSC. The submission took a market share approach to estimating financial impact, based on the assumption that BFTAF would only displace FTAF regimens.

**Table 10: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed						
<b>Estimated financial implications of BFTAF</b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for FTAF treatments</b>						
Cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	-\$	-\$	-\$	-\$	-\$	-\$
<b>Net financial implications</b>						
Net cost to PBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$

BFTAF = bicitgravir, emtricitabine and tenofovir alafenamide, FTAF = emtricitabine and tenofovir alafenamide; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Tables 4.3, 4.6, 4.7, 4.8, 4.10, 4.11, and 4.12, p105-110 of the submission

The redacted table shows that at Year 6, the estimated number of scripts dispensed was 10,000 – 50,000 per year.

- 6.36 The submission estimated overall net savings to the PBS/RPBS of less than \$10 million in Year 1 increasing to \$10 - \$20 million in Year 6. The submission did not estimate any costs to other government health budgets.

- 6.37 Savings would be expected to change based on the relative replacement of DESCOVY® plus dolutegravir (more expensive than BFTAF) versus GENVOYA® and ODEFSEY® (cost neutral) and whether other less expensive, but relevant, alternative therapies are replaced. The ESC considered that TAF-based therapies would constitute the bulk of displacement by BFTAF and other therapies would likely be replaced to a smaller extent.
- 6.38 The Pre-PBAC Response reiterated the cost savings to be gained through BFTAF listing by displacement of DESCOVY® + dolutegravir from the market share, but acknowledged that the magnitude of savings would be expected to change based on the relative displacement of DESCOVY® + dolutegravir versus GENVOYA® and ODEFSEY®.

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

## **7 PBAC outcome**

- 7.1 The PBAC was of a mind to recommend the Authority Required (STREAMLINED) Section 100 listing for a fixed dose combination (FDC) tablet containing tenofovir alafenamide with emtricitabine and bictegravir (BFTAF) for the treatment of patients with human immunodeficiency virus (HIV-1). However the PBAC deferred making a final recommendation pending the provision of the relevant TGA delegate's overview.
- 7.2 The PBAC considered that the cost-effectiveness of BFTAF would be acceptable if it were cost-minimised against the lowest priced alternative FDC triple-therapy for the treatment of HIV (i.e. tenofovir disoproxil-based (TDF) alternatives to the nominated secondary comparators GENVOYA® and ODEFSEY®, STRIBILD® and EVIPLERA®). The equi-effective doses are:
- bictegravir 50 mg /emtricitabine 200 mg/ tenofovir alafenamide 25 mg in an FDC product;
  - STRIBILD® (tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg/ elvitegravir 150 mg/cobicistat 250 mg in an FDC product); and
  - EVIPLERA® (tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg/ rilpivirine 25 mg in an FDC product).
- 7.3 The PBAC accepted the nominated comparators of DESCOVY® plus dolutegravir, GENVOYA® and ODEFSEY®. However, the PBAC considered that all alternative FDC triple-therapies for the treatment of HIV are relevant alternative therapies given that accepted relativities and evidence presented in the trial both support a claim of non-inferiority to these therapies. Accordingly, the PBAC considered that a cost-minimisation approach against the least expensive FDC triple-therapy regimen for the treatment of HIV would be required to satisfy the requirements of Section 101 (3B) of the *National Health Act 1953*.
- 7.4 The PBAC recommended that the restriction for BFTAF should be consistent with

that of GENVOYA® and ODEFSEY®, and that it should therefore include both treatment-experienced and treatment-naïve patients.

- 7.5 The PBAC noted that the primary trials (Trial 1490 and 1878) reported the proportion of patients with HIV ribonucleic (RNA) < 50 copies/mL (as per the FDA snapshot algorithm) as the clinically relevant outcome. The PBAC also noted that, in terms of safety, similar adverse events were experienced in treatment-naïve patients treated with BFTAF or DESCOVY® + dolutegravir (Trial 1490). Although the PBAC noted higher proportions of select emergent adverse events were reported with BFTAF compared to regimens with a TRUVADA®- or KIVEXA®- backbone (Trial 1878), the PBAC considered that the safety of BFTAF was overall similar noting there were no major safety signals in patients treated with BFTAF. The PBAC noted that this data was informative and considered that the claims of non-inferior efficacy and safety of BFTAF over DESCOVY® + dolutegravir, GENVOYA® and ODEFSEY®, and also to TRIUMEQ®, TRUVADA®- and KIVEXA®-based regimens in was supported.
- 7.6 The PBAC advised that BFTAF is not suitable for prescribing by nurse practitioners.
- 7.7 The PBAC formed the view that the Early Supply Rule should apply to BFTAF, as recommended for all HIV treatments at the November 2015 meeting.
- 7.8 The PBAC noted that this submission is eligible for an Independent Review.

**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**

Gilead notes that the PBAC accepted that the nominated comparators of DESCOVY® plus dolutegravir, GENVOYA® and ODEFSEY® were appropriate. These are the regimens that it is agreed are most likely to be replaced in clinical practice. Older fixed dose regimens have been superseded by newer, safer treatments and no longer represent alternative therapies.

**Addendum to the March 2018 PBAC Minutes:**

**4.01 BICTEGRAVIR + EMTRICITABINE + TENOFOVIR  
ALAFENAMIDE FIXED DOSE COMBINATION,  
Tablet containing tenofovir alafenamide 25 mg with  
emtricitabine 200 mg and bicitegravir 50 mg,  
Biktarvy®  
Gilead Sciences Pty Ltd**

**Preface**

To improve the readability of this addendum, brand names are generally used to identify fixed dose combination (FDC) antiretroviral products.

**Background**

- 9.1 At the March 2018 meeting, the PBAC deferred making a recommendation on the listing for a fixed dose combination (FDC) tablet containing tenofovir alafenamide with emtricitabine and bicitegravir (BIKTARVY®) for the treatment of patients with human immunodeficiency virus (HIV-1). The PBAC was of a mind to recommend the listing of BIKTARVY® pending the provision of the relevant TGA delegate's overview.
- 9.2 At that time, the PBAC considered that the cost-effectiveness of BIKTARVY® would be acceptable if it were cost-minimised against STRIBILD® and EVIPLERA®.
- 9.3 At that time the PBAC considered that all FDC triple-therapies for the treatment of HIV were alternative therapies to BIKTARVY®.

**Current situation**

- 9.4 Subsequent to the March 2018 PBAC meeting, the sponsor provided the TGA delegate's overview which outlined the delegate's intent to approve BIKTARVY® for the treatment of HIV-1 infection in adults who are ART-naïve or virologically suppressed without any known mutations associated with resistance to the individual components of BIKTARVY®.
- 9.5 The sponsor's pre-PBAC Response maintained its previous argument (to the March 2018 meeting of PBAC) that GENVOYA® and ODEFSEY® are the lowest cost, most appropriate and relevant comparators for BIKTARVY® for the purpose of Section 101 (3B) of the *National Health Act 1953* (the Act). The pre-PBAC Response argued that

the selection of GENVOYA® and ODEFSEY® as the lowest cost comparator is consistent with current guidelines and clinical practice of first selecting the backbone for the antiretroviral therapy regimen (ART), and then the third agent whereas the PBAC's advice that the lowest price alternative therapies are STRIBILD® and EVIPLERA® is not consistent with clinical practice.

- 9.6 The pre-PBAC Response further argued that BIKTARVY®, for some patients, provides a significant improvement in efficacy or reduction in toxicity over STRIBILD® and EVIPLERA®. The PSCR also asserted that TAF-based regimens could be used in some patients in whom TDF-based regimens (such as STRIBILD® and EVIPLERA®) cannot, specifically patients with renal impairment. Additionally, the pre-PBAC Response cited findings from the EuroSIDA study, a multicentre prospective study of more than 16,000 patients across Europe, Israel and Argentina that report that TDF use was associated with a 16% increase in chronic kidney disease<sup>1</sup>.
- 9.7 The Pre-PBAC Response reiterated that the listing of BIKTARVY® will result in significant cost-saving to the PBS budget, estimated at \$60 - \$100 million over the first six years of listing due to substitution of DESCOVY® plus dolutegravir.

## 10 PBAC Outcome

- 10.1 The PBAC recommended the Authority Required (STREAMLINED) Section 100 (Community Access) listing of tenofovir alafenamide with emtricitabine and bictegravir (BIKTARVY®) in a fixed dose combination tablet on the basis that it should be available only under the special arrangements and circumstances described in the table at section 11 below.
- 10.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of BIKTARVY® would be acceptable if it were cost-minimised against a mixed comparator of EVIPLERA®/STRIBILD® and GENVOYA®/ODEFSEY®. The latter component of the price accounting for the small patient population (6% of the total population) ineligible to receive a tenofovir disoproxil fumarate (TDF) based regimen due to moderate or severe renal impairment for which TDF is not recommended.
- 10.3 The equi-effective doses are
- BIKTARVY® (bictegravir 50 mg /emtricitabine 200 mg/ tenofovir alafenamide 25 mg);
  - STRIBILD® (tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg/ elvitegravir 150 mg/cobicistat 150 mg);
  - EVIPLERA® (tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg/

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<sup>1</sup> Mallipattu, SK., Wyatt, CM and He, JC., 2012. The New Epidemiology of HIV-Related Kidney Disease. Journal of AIDS & clinical research, Suppl 4:001-. doi:10.4172/2155-6113.S4-001.

- rilpivirine 25 mg);
  - GENVOYA® (tenofovir alafenamide 10 mg/ emtricitabine 200 mg/ elvitegravir 150 mg / cobicistat 150 mg; and
  - ODEFSEY® (emtricitabine 200 mg/ rilpivirine 25 mg/ tenofovir alafenamide 25 mg
- 10.4 The PBAC noted that Australian data on renal impairment, as defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min, in human immune deficiency virus (HIV) patients<sup>2</sup> estimated approximately 6% of patients have an eGFR below this level, and would therefore be ineligible to receive TDF containing regimens.
- 10.5 The PBAC recalled that it was of a mind to recommend the listing of BIKARVY® at the March 2018 meeting pending the provision of the relevant TGA delegate’s overview that had now been issued.
- 10.6 The PBAC recalled that in March 2018 it considered all alternative FDC triple-therapies for the treatment of HIV were alternative therapies to BIKTARVY. It also concluded at that time that accepted relativities and evidence supported a claim of non-inferiority of BIKTARVY to each of those therapies. Upon reconsideration, the PBAC accepted that its earlier conclusion in that regard was incorrect in that TRIZIVIR® (abacavir, lamivudine & zidovudine) has not been demonstrated to be non-inferior in terms of efficacy and toxicity to other FDC triple-therapies. In addition, the PBAC noted there is now considerable evidence that efavirenz (a component of Atripla®) is associated with a range of moderate-to-severe central nervous system (CNS) adverse events including drowsiness, insomnia, nightmares, agitation, memory loss, hallucinations and other effects. The PBAC was therefore satisfied that therapies containing efavirenz are of inferior safety to non-efavirenz containing therapies for the treatment of HIV infection.
- 10.7 The PBAC considered the sponsor’s arguments that GENVOYA® and ODEFSEY® are the appropriate lowest cost comparators. However, the PBAC did not accept that, because TDF containing regimens could not be used in the sub-group of patients with renal impairment, these regimens could not be considered as potential alternative therapies for the remainder of the broader target population.
- 10.8 As noted in paragraph 10.4 above, the PBAC agreed with the submission in the pre-PBAC Response that there is a subgroup of patients with renal impairment in whom TDF containing regimens should not be considered an alternative therapy to BIKARVY®. The PBAC considered that the alternative therapies to BIKARVY® in patients with renal impairment are GENVOYA® and ODEFSEY®.

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<sup>2</sup> Gracey, D., Chan, D., Bailey, M., Richards, D. and Dalton, B., 2013. Screening and management of renal disease in human immunodeficiency virus-infected patients in Australia. Internal medicine journal, 43(4), pp.410-416.

- 10.9 However, the PBAC considered that the TDF containing regimens, STRIBILD® and EVIPLERA® are alternative therapies to BIKARVY® in patients who do not have renal impairment.
- 10.10 The PBAC recalled that it had recommended GENVOYA® on a cost-minimisation basis with STRIBILD (GENVOYA®, November 2015 Public Summary Document). The PBAC further recalled that at the time it had recommended GENVOYA®, it had not been satisfied that GENVOYA® provided, for any group of patients, a significant improvement in patient compliance or efficacy, or a significant reduction in toxicity over alternative therapies. In particular, the PBAC considered there remained uncertainty that changes in surrogate outcomes of bone and renal safety over a 48-week study period were sufficient to support the claimed significant reduction in toxicity in some patients over a lifetime. The PBAC noted the sponsor had not made a further submission seeking to change the PBAC's previously expressed view.
- 10.11 The PBAC further recalled that in July 2016 it had formed the view that ODEFSEY® is non inferior to EVIPLERA® in terms of effectiveness and safety (ODEFSEY® July 2016 Public Summary Document). The PBAC recalled that at the time, it had not been satisfied that ODEFSEY® provided, for any group of patients, a significant improvement in patient compliance or efficacy, or a significant reduction in toxicity, over alternative therapies. In particular, the PBAC considered there remained uncertainty that changes in surrogate outcomes of bone and renal safety over a 96-week study period were sufficient to support the claimed significant reduction in toxicity in some patients over a lifetime. The PBAC noted the sponsor had not made a further submission seeking to change the PBAC's previously expressed view.
- 10.12 The PBAC agreed with the Pre-PBAC Response that the listing of BIKTARVY® would result in a net saving to the PBS, however the PBAC considered the utilisation estimates (less than \$10 million in Year 1 increasing to \$10 - \$20 million in Year 6) in the March 2018 submission to be uncertain as this would be expected to change based on the relative replacement of DESCOVY® plus dolutegravir versus GENVOYA® and ODEFSEY® and whether other less expensive, but relevant, alternative therapies are replaced.
- 10.13 The PBAC reiterated that the restriction for BIKTARVY® should be consistent with that of GENVOYA® and ODEFSEY®, and that it should therefore include both treatment-experienced and treatment-naïve patients.
- 10.14 The PBAC advised that BFTAF should not be treated as interchangeable on an individual basis with any other drugs.
- 10.15 The PBAC advised that BFTAF is not suitable for prescribing by nurse practitioners.
- 10.16 The PBAC recommended that the Early Supply Rule should apply to BFTAF, as recommended for all HIV treatments at the November 2015 meeting.
- 10.17 The PBAC noted that this submission is not eligible for an Independent Review as it

received a positive recommendation.

**Outcome:**

Recommended

## 11 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BICTEGRAVIR+EMTRICITABINE+TENOFIVIR ALAFENAMIDE 50MG+200MG+25MG, TABLET.	2	5	BIKTARVY®

<b>Category/Program:</b>	Section 100 Community Access
<b>Condition:</b>	HIV infection
<b>PBS Indication:</b>	HIV infection
<b>Treatment phase:</b>	Initial
<b>Restriction:</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>Treatment phase:</b>	Continuing
<b>Restriction</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.

## 12 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.

## 13 Sponsor’s Comment

The sponsor had no comment.