

## Product Information

### DESCOVY<sup>®</sup> (emtricitabine/tenofovir alafenamide) tablets

#### NAME OF THE MEDICINE

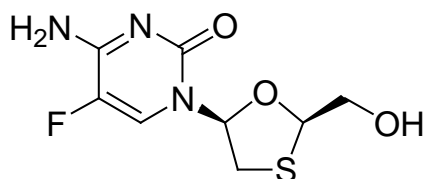
DESCOVY (200 mg emtricitabine/25 mg tenofovir alafenamide) and DESCOVY 200 mg emtricitabine/10 mg tenofovir alafenamide ) tablets.

The drug substances in DESCOVY tablets are emtricitabine (FTC) and tenofovir alafenamide (TAF) fumarate.

EMTRIVA<sup>®</sup> is the brand name for FTC, a synthetic nucleoside analog of cytidine. TAF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

**Emtricitabine:** The chemical name of FTC is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. FTC is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of C<sub>8</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>3</sub>S and a molecular weight of 247.2. It has the following structural formula:



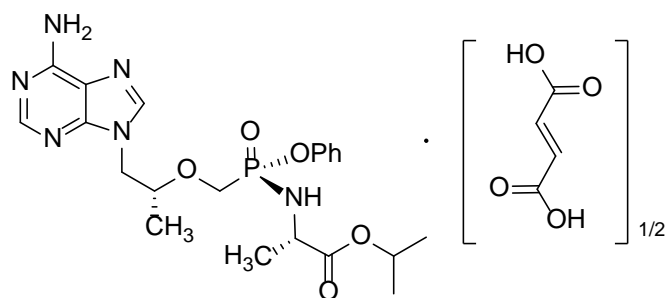
CAS registry number: 143491-57-0

FTC is a white to off-white crystalline powder with a solubility of approximately 112 mg per mL in water at 25 °C. The partition coefficient (*log p*) for emtricitabine is -0.43 and the pK<sub>a</sub> is 2.65.

**Tenofovir Alafenamide Fumarate:** The chemical name of tenofovir alafenamide fumarate is L-Alanine, *N*-[(*S*)-[[(*1R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

It has an empirical formula of C<sub>21</sub>H<sub>29</sub>O<sub>5</sub>N<sub>6</sub>P•½(C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) and a molecular weight of 534.50. It has the following structural formula:

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**



CAS registry number for tenofovir alafenamide: 379270-37-8

CAS registry number for tenofovir alafenamide fumarate: 1392275-56-7

TAF is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

## DESCRIPTION

**DESCOVY 200/25 mg tablets** contain the following ingredients as excipients:

*Tablet core:* microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

*Film-coating:* polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and indigo carmine aluminum lake.

Each 200/25 mg DESCOVY tablet is rectangular shaped, film-coated and blue in colour. Each tablet is debossed with 'GSI' on one side and the number "225" on the other side. The tablets are supplied in bottles with child resistant closures.

**DESCOVY 200/10 mg tablets** contain the following ingredients as excipients:

*Tablet core:* microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

*Film-coating:* polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide black.

Each 200/10 mg DESCOVY tablet is rectangular shaped, film-coated and gray in colour. Each tablet is debossed with 'GSI' on one side and the number "210" on the other side. The tablets are supplied in bottles with child resistant closures.

## PHARMACOLOGY

*Pharmacotherapeutic group:* Antivirals for treatment of HIV infections, combinations, ATC code: J05AF30.

### Mechanism of action

DESCOVY is a fixed-dose combination tablet containing the antiviral drugs FTC and TAF.

**Emtricitabine:** FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

FTC has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase  $\gamma$  and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

**Tenofovir Alafenamide:** TAF is a phosphoramidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than tenofovir disoproxil fumarate (TDF) in loading tenofovir into peripheral blood mononuclear cells (PBMCs), including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus (HBV). *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase  $\gamma$  and there is no evidence of toxicity to mitochondria *in vitro*.

#### **Antiviral activity *in vitro***

**Emtricitabine:** The *in vitro* antiviral activity of FTC against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The EC<sub>50</sub> values for emtricitabine were in the range of 0.0013 to 0.64  $\mu$ M (0.0003 to 0.158  $\mu$ g per mL).

FTC displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (EC<sub>50</sub> values ranged from 0.007 to 0.075  $\mu$ M) and showed strain specific activity against HIV-2 (IC<sub>50</sub> values ranged from 0.007 to 1.5  $\mu$ M).

In drug combination studies of FTC with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (PI) (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. No antagonism was observed for these combinations.

**Tenofovir Alafenamide:** The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC<sub>50</sub> values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC<sub>50</sub> values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC<sub>50</sub> values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

## Drug Resistance

### In Cell Culture:

**Emtricitabine:** HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

**Tenofovir Alafenamide:** HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, FTC, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with TAF have shown no development of high-level resistance after extended culture.

### In Clinical Studies:

**In Treatment-Naïve Patients:** In a pooled analysis of antiretroviral-naïve patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet in GS-US-292-0104, GS-US-292-0111, and a Phase 2 study (GS-US-292-0102), genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA > 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. As of Week 48, the development of one or more primary FTC, TAF, or EVG resistance-associated mutations was observed in 7 of 14 patients with evaluable genotypic data from paired baseline and EVG+COBI+FTC+TAF treatment-failure isolates (7 of 978 patients [0.7%]) compared with 7 of 15 treatment-failure isolates from patients in the EVG+COBI+FTC+TDF group (7 of 925 patients [0.8%]). Of the 7 patients with resistance development in the EVG+COBI+FTC+TAF group, the mutations that emerged were M184V/I (N = 7) and K65R (N = 1) in reverse transcriptase and T66T/A/I/V (N = 2), E92Q (N = 2), Q148Q/R (N = 1), and N155H (N = 1) in integrase. Of the 7 patients with resistance development in the EVG+COBI+FTC+TDF group, the mutations that emerged were M184V/I (N = 7) and K65R (N = 2) in reverse transcriptase and E92E/Q (N = 3) and Q148R (N = 2) in integrase. All patients in both treatment groups who developed resistance to EVG in integrase also developed resistance mutations to FTC in reverse transcriptase.

In phenotypic analyses of patients in the resistance analysis population, 6 of 14 patients (43%) receiving EVG+COBI+FTC+TAF had HIV-1 isolates with reduced susceptibility to FTC compared with 5 of 15 patients (33%) receiving EVG+COBI+FTC+TDF. No patient receiving either treatment had HIV-1 isolates with reduced susceptibility to tenofovir. Finally, 4 of 14 patients (29%) had reduced susceptibility to EVG in the EVG+FTC+FTC+TAF group compared with 4 of 15 patients (27%) in the EVG+FTC+FTC+TDF group.

**In Virologically Suppressed Patients:** In a Week 48 analysis of virologically-suppressed patients who switched from TRUVADA to DESCOVY while maintaining their third antiretroviral agent (GS-US-311-1089), 1 of 2 patients analysed in the DESCOVY +third

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

agent group (1 of 333 [0.3%]) developed M184V in reverse transcriptase with reduced susceptibility to emtricitabine.

In the TRUVADA+third agent group, 0 of 1 patients analysed (0 of 330 [0%]) developed resistance to any components of their regimen.

No emergent resistance to FTC or TAF was identified in a clinical study of virologically-suppressed patients who switched from a regimen containing FTC+TDF to FTC+TAF given with EVG+COBI in a fixed-dose combination tablet (GS-US-292-0109, N = 799).

### **Cross-resistance:**

**Emtricitabine:** FTC-resistant isolates (M184V/I) were cross-resistant to 3TC but retained sensitivity to didanosine, d4T, tenofovir and AZT.

Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT - thymidine analogue-associated mutations - TAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation or substitutions associated with resistance to NNRTI were susceptible to emtricitabine.

**Tenofovir Alafenamide:** The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, FTC, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to TAF.

HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs were susceptible to TAF.

HIV-1 containing mutations associated with resistance to PIs, such as M46I, I54V, V82F/T, and L90M were susceptible to TAF.

### **Pharmacodynamics**

#### **Effects on Electrocardiogram**

In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a suprathreshold dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component, FTC, or the combination of FTC and TAF on the QT interval is not known.

#### **Pharmacokinetics**

#### **Bioequivalence**

FTC and TAF exposures were bioequivalent when comparing DESCOVY 200/25 mg to GENVOYA (EVG/COBI/FTC/TAF [150/150/200/10 mg] fixed-dose combination tablet) following single-dose administration to healthy subjects (N=116) under fed conditions.

FTC and TAF exposures were bioequivalent when comparing DESCOVY 200/10 mg, administered simultaneously with EVG 150 mg and COBI 150 mg, to GENVOYA(EVG/COBI/FTC/TAF) [150/150/200/10 mg] fixed-dose combination tablet) following single-dose administration to healthy subjects (N=100) under fed conditions.

### **Absorption and Bioavailability**

Following oral administration with food in HIV-1 infected adult patients, peak plasma concentrations were observed 3 hours post-dose for FTC and 1 hour post-dose TAF (see Table 1 for additional pharmacokinetic parameters).

**Table 1. Pharmacokinetic Parameters of FTC and TAF Exposure Following Oral Administration in HIV-Infected Adults**

<b>Parameter Mean ± SD [range: min:max]</b>	<b>FTC<sup>a</sup></b>	<b>TAF<sup>b</sup></b>
$C_{max}$ (mg/mL)	1.9 ± 0.5 [0.6:3.6]	0.16 ± 0.08 [0.02:0.97]
AUC <sub>tau</sub> (mg/h/ mL)	12.7 ± 4.5 [5.2:34.1]	0.21 ± 0.15 [0.05:1.9]
$C_{trough}$ (mg/ mL)	0.14 ± 0.25 [0.04:1.94]	NA

SD = Standard Deviation; NA = Not Applicable

- a. From Intensive Pharmacokinetic analysis, N=61-62
- b. From Population Pharmacokinetic analysis, N=539.

### **Effect of Food on Oral Distribution**

Relative to fasting conditions, administration of DESCOVY with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in emtricitabine  $C_{max}$  and AUC<sub>last</sub> of 27% and 9%, respectively; and a decrease in TAF  $C_{max}$  (15-37%) and an increase in AUC<sub>last</sub> (17-77%). These changes are not considered clinically meaningful and DESCOVY can be administered without regard to food.

### **Distribution, Metabolism and Elimination**

**Emtricitabine:** *In vitro* binding of FTC to human plasma proteins is < 4% and is independent of concentration over the range of 0.02 to 200 µg per mL. Following administration of radiolabelled FTC approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. FTC is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

**Tenofovir Alafenamide:** *In vitro* binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01 to 25 µg per mL. Ex-vivo binding of TAF to human plasma proteins in samples collected during clinical studies was approximately 80%.



**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

Distribution studies in dogs showed 5.7 to 15-fold higher <sup>14</sup>C-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [<sup>14</sup>C]-TAF relative to [<sup>14</sup>C]-TDF.

Metabolism is a major elimination pathway for TAF in humans, accounting for > 80% of an oral dose. *In vitro* Studies have shown that TAF is metabolized to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of TAF resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of TDF.

*In vitro*, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is minimally metabolized by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was not significantly affected. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1 *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

TAF is eliminated following metabolism to tenofovir. TAF and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of intact TAF is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150 to 180 hours within PBMCs.

### **Age, Gender and Ethnicity**

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for FTC or TAF.

Pharmacokinetics of FTC and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Population pharmacokinetics analysis of HIV-infected patients in Phase 2 and Phase 3 studies of FTC+TAF given with EVG+COBI as a fixed dose combination tablet showed that within the age range studied (12 to 82 years), age did not have a clinically relevant effect on exposures of TAF.

Exposures of FTC and TAF achieved in 24 paediatric patients aged 12 to < 18 years were similar to exposures achieved in treatment-naïve adults.

### **Patients with Impaired Renal Function**

No clinically relevant differences in TAF, or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated creatinine clearance less than 30 mL per min) in studies of TAF. There are no pharmacokinetic data on TAF in subjects with estimated creatinine clearance less than 15 mL per min.

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

The safety, virologic, and immunologic responses of DESCOVY in HIV-1 infected patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30 - 69 mL per min) are based on an open label trial (Study 112) that evaluated FTC+TAF given with EVG+COBI as a fixed dose combination tablet in 242 virologically suppressed patients and 6 treatment-naïve patients. The safety profile of DESCOVY in subjects with mild to moderate renal impairment was similar to safety data from patients with normal renal function.

### **Patients with Hepatic Impairment**

The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of TAF has not been studied.

**Emtricitabine:** The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

**Tenofovir Alafenamide:** Clinically relevant changes in tenofovir pharmacokinetics in patients with hepatic impairment were not observed in patients with mild to moderate hepatic impairment, and no TAF dose adjustment is required in patients with mild to moderate hepatic impairment.

### **Hepatitis B and/or hepatitis C virus co-infection**

Pharmacokinetics of FTC and TAF have not been fully evaluated in hepatitis B and/or C co-infected patients.

### **Assessment of Drug Interactions**

**Emtricitabine:** *In vitro* and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. FTC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of FTC.

In drug interaction studies conducted with FTC and with TDF, coadministration of FTC and famciclovir had no effect on the  $C_{max}$  or AUC of either drug.

**Tenofovir Alafenamide:** TAF is transported by P-glycoprotein (P-gp). Drugs that strongly affect P-gp activity may lead to changes in TAF absorption.

TAF is not an inhibitor or inducer of CYP3A *in vivo*.

### **Drug Interaction Studies**

Drug-drug interaction studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) as individual agents.



**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

The effects of coadministered drugs on the exposure of TAF are shown in Table 2. The effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 3.

**Table 2 Drug Interactions: Changes in Pharmacokinetic Parameters for TAF in the Presence of the Coadministered Drug<sup>a</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI) <sup>b</sup> ; No effect = 1.00		
				C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir	300 + 100 ritonavir once daily	10 once daily	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150 daily	8 once daily	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 + 150 cobicistat once daily	25 once daily	11	0.93 (0.72, 1.21) <sup>d</sup>	0.98 (0.80, 1.19) <sup>d</sup>	NC
Darunavir	800 + 100 ritonavir once daily	10 once daily	10	1.42 (0.96, 2.09) <sup>e</sup>	1.06 (0.84, 1.35) <sup>e</sup>	NC
Dolutegravir	50 once daily	10 once daily	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600 once daily	40 once daily <sup>c</sup>	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800/200 ritonavir once daily	10 once daily	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25 once daily	25 once daily	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 once daily	10 once daily	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. All No Effect Boundaries are 70% -143% unless otherwise specified.

c. Study conducted with DESCOVY (FTC/TAF).

d. Mean ratio of tenofovir PK parameters (90% CI) was 3.16 (3.00, 3.33) for C<sub>max</sub>, 3.24 (3.02, 3.47) for AUC, and 3.21 (2.90, 3.54) for C<sub>min</sub>.

e. Mean ratio of tenofovir PK parameters (90% CI) was 2.42 (1.98, 2.95) for C<sub>max</sub>, 2.43 (2.07, 2.84) for AUC<sub>last</sub>.

f. Study conducted with GENVOYA.

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

**Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TAF<sup>a</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir	300 +100 ritonavir once daily	10 once daily	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Cobicistat	150 once daily	8 once daily	14	1.06 (1.00, 1.12)	1.09 (1.03, 1.15)	1.11 (0.98, 1.25)
Darunavir	800 + 150 cobicistat once daily	25 once daily <sup>c</sup>	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 + 100 ritonavir once daily	10 once daily	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 once daily	10 once daily	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800/200 ritonavir once daily	10 once daily	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam <sup>d</sup>	2.5 once daily, orally	25 once daily	18	1.02 (0.92, 1.13)	1.12 (1.03, 1.22)	NC
	1 once daily IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25 once daily	25 once daily	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 single dose	10 once daily <sup>e</sup>	19	1.14 (0.94, 1.38)	1.09 (0.90, 1.32)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. All No Effect Boundaries are 70% -143% unless otherwise specified.

c. Study conducted with DESCOVY (FTC/TAF).

d. A sensitive CYP3A4 substrate.

e. Study conducted with GENVOYA.

**CLINICAL TRIALS**

The efficacy and safety of DESCOVY in HIV-1 infected, treatment-naïve adults are based on 96-week data from two randomized, double-blind, active-controlled studies, GS-US-292-0104 (Study 104) and GS-US-292-0111 (Study 111) (N=1733). The efficacy and safety of DESCOVY in virologically-suppressed HIV-1 infected adults is based on 48-week data from a randomized, open-label, active-controlled study, GS-US-292-0109 ( N = 1436) and a randomised, double-blind, active-controlled study GS-US-311-1089 (Study 1089) (N=663). The efficacy and safety of DESCOVY in HIV-1 infected, virologically-suppressed patients with mild to moderate renal impairment are based on 72-week data from an open-label study, GS-US-292-0112 (Study 112) (N=242). The efficacy and safety of DESCOVY in HIV-1 infected, treatment-naïve pediatric patients between the ages of 12 to < 18 years is based on 48-week data from an open-label study, GS-US-292-0106 (Study 106) (N=50).

**Treatment-Naïve Patients**

In both Study 104 and Study 111, patients were randomized in a 1:1 ratio to receive either DESCOVY (N = 866) once daily or FTC+TDF ( N = 867) once daily, both given with EVG+COBI as a fixed dose combination tablet.

In Studies 104 and 111, the mean age was 36 years (range 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 log<sub>10</sub> copies per mL (range 1.3–7.0). The mean baseline CD4+ cell count was 427 cells per mm<sup>3</sup> (range 0-1360) and 13% had CD4+ cell counts less than 200 cells per mm<sup>3</sup>. Twenty-three percent of patients had baseline viral loads greater than 100,000 copies per mL.

In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL, greater than 100,000 copies per mL to less than or equal to 400,000 copies per mL, or greater than 400,000 copies per mL), by CD4 count (less than 50 cells per µL, 50-199 cells per µL, or greater than or equal to 200 cells per µL), and by region (US or ex-US).

Treatment outcomes of Studies 104 and 111 through 96 weeks are presented in Table 4.

**Table 4 Pooled Virologic Outcomes of Studies 104 and 111 at Weeks 48<sup>a</sup> and 96<sup>b</sup>**

	<b>FTC+TAF (Administered asGENVOYA) (N=866)</b>	<b>FTC+TDF (Administered as STRIBILD) (N=867)</b>	<b>FTC+TAF (Administered as GENVOYA) (N=866)</b>	<b>FTC+TDF (Administered as STRIBILD) (N=867)</b>
	<b>Week 48</b>		<b>Week 96</b>	
<b>HIV-1 RNA &lt; 50 copies/mL</b>	92%	90%	87%	85%
Treatment Difference	2.0% (95% CI: -0.7% to 4.7%)		1.5% (95% CI = -1.8% to 4.8%)	
<b>HIV-1 RNA ≥ 50 copies/mL<sup>c</sup></b>	4%	4%	5%	4%
<b>No Virologic Data at Week 48 or 96 Window</b>	4%	6%	9%	11%

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

	<b>FTC+TAF (Administered asGENVOYA) (N=866)</b>	<b>FTC+TDF (Administered as STRIBILD) (N=867)</b>	<b>FTC+TAF (Administered as GENVOYA) (N=866)</b>	<b>FTC+TDF (Administered as STRIBILD) (N=867)</b>
	<b>Week 48</b>		<b>Week 96</b>	
Discontinued Study Drug Due to AE or Death <sup>d</sup>	1%	2%	1%	2%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL <sup>e</sup>	2%	4%	6%	7%
Missing Data During Window but on Study Drug	1%	< 1%	2%	1%

**Proportion (%) of Patients with HIV-1 RNA < 50 copies/mL by Subgroup**

<b>Age</b>				
< 50 years	716/777 (92%)	680/753 (90%)	668/777 (86%)	639/753 (85%)
≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	100/114 (88%)
<b>Sex</b>				
Male	674/733 (92%)	673/740 (91%)	635/733 (87%)	631/740 (85%)
Female	126/133 (95%)	111/127 (87%)	115/133 (86%)	108/127 (85%)
<b>Race</b>				
Black	197/223 (88%)	177/213 (83%)	173/223 (78%)	168/213 (79%)
Nonblack	603/643 (94%)	607/654 (93%)	577/643 (90%)	571/654 (87%)
<b>Baseline Viral Load</b>				
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)	587/670 (88%)	573/672 (85%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)	163/196 (83%)	166/195 (85%)
<b>Baseline CD4+ cell count</b>				
< 200 cells per mm <sup>3</sup>	96/112 (86%)	104/117 (89%)	93/112 (83%)	97/117 (83%)
≥ 200 cells per mm <sup>3</sup>	703/753 (93%)	680/750 (91%)	657/753 (87%)	642/750 (86%)

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

- Week 48 window was between Day 294 and 377 (inclusive)
- Week 96 window was between Day 630 and 713 (inclusive)
- Included patients who had  $\geq 50$  copies per mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of  $\geq 50$  copies per mL.
- Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
- Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

FTC+TAF met the noninferiority criteria in achieving HIV-1 RNA  $< 50$  copies per mL when compared to FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet.

The mean increase from baseline in CD4+ cell count at Week 96 was 280 cells per  $\text{mm}^3$  in patients receiving FTC+TAF and 266 cells/ $\text{mm}^3$  in patients receiving FTC+TDF ( $p = 0.14$ ).

**Bone Mineral Density:** In the pooled analysis of Studies 104 and 111, bone mineral density (BMD) from baseline to Week 96 was assessed by dual-energy X-ray absorptiometry (DXA) to compare the bone safety of TAF to that of TDF. As shown in Table 5, in patients who had both baseline and Week 96 hip or spine measurements (N= 722 in the FTC+TAF group and N = 714 in the FTC+TDF group) there were smaller decreases in BMD in patients receiving FTC+TAF as compared with FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet.

**Table 5 Measures of Bone Mineral Density in Studies 104 and 111 (Week 96 analysis)**

	<b>FTC+TAF (Administered as GENVOYA)</b>	<b>FTC+TDF (Administered as STRIBILD)</b>	<b>Treatment Difference</b>
<b>Hip DXA Analysis</b>	N=716	N=711	
Mean Percent Change in BMD	-0.7%	-3.3%	2.60% p < 0.001
Subjects with Categorical Change: > 3% Decrease in BMD	23%	56%	--
> 3% Increase in BMD	12%	6%	
Subjects with No Decrease in BMD	39%	16%	--
<b>Lumbar Spine DXA Analysis</b>	N=722	N=714	
Mean Percent Change in BMD	-1.0%	-2.8%	1.83% p < 0.001
Subjects with Categorical Change: >3% Decrease in BMD	26%	48%	--
>3% Increase in BMD	11%	6%	
Subjects with No Decrease in BMD	37%	21%	--

**Changes in Renal Laboratory Tests:** In the pooled analysis of Studies 104 and 111, laboratory tests were performed to compare the effect of TAF, to that of TDF on renal safety. As shown in Table 6, statistically significant differences were observed between treatment groups that favored TAF for increases in serum creatinine and changes in proteinuria, including Urine Protein to Creatinine Ratio (UPCR), Urine Albumin to Creatinine Ratio

(UACR), urinary retinol binding protein (RBP) to creatinine ratio, and beta-2-microglobulin to creatinine ratio.

**Table 6 Change from Baseline in Renal Laboratory Tests in Studies 104 and 111 (Week 96 analysis)**

	<b>FTC+TAF (Administered as GENVOYA) N=866</b>	<b>FTC+TDF (Administered as STRIBILD) N=867</b>	<b>P Value</b>
Serum Creatinine (mg/dL) <sup>a</sup>	0.04 ± 0.11	0.07 ± 0.13	p < 0.001
Proteinuria by Urine Dipstick <sup>b</sup>	36%	41%	p = 0.034
Urine Protein to Creatinine Ratio [UPCR] <sup>c</sup>	-9.1%	16.2%	p < 0.001
Urine Albumin to Creatinine Ratio [UACR] <sup>c</sup>	-5.2%	4.9%	p < 0.001
Urine RBP to Creatinine Ratio <sup>c</sup>	13.8%	74.2%	p < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio <sup>c</sup>	-32.1%	33.5%	p < 0.001

a. Mean change ± SD.

b. Includes all severity grades (1-4).

c. Median percent change.

### **Virologically-Suppressed Patients**

#### **Study 109**

In Study 109, the efficacy and safety of switching from either ATRIPLA<sup>®</sup>, TRUVADA<sup>®</sup> plus atazanavir (boosted by either COBI or ritonavir), or STRIBILD<sup>®</sup> to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet were evaluated in a randomized, open-label trial of virologically-suppressed (HIV-1 RNA < 50 copies per mL) HIV-1 infected adults (N = 1436). Patients must have been stably suppressed (HIV-1 RNA < 50 copies per mL) on their baseline regimen for at least 6 months and had no resistance mutations to FTC, TAF or EVG prior to study entry. Patients were randomized in a 2:1 ratio to either switch to FTC+TAF, given with EVG+COBI as a fixed-dose combination tablet at baseline (N=959), or stay on their baseline antiretroviral regimen (N=477). Patients had a mean age of 41 years (range 21-77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/mm<sup>3</sup> (range 79-1951).

Patients were stratified by prior treatment regimen. At screening, 42% of patients were receiving TRUVADA plus atazanavir (boosted by either COBI or ritonavir), 32% of patients were receiving STRIBILD, and 26% of patients were receiving ATRIPLA.

Treatment outcomes of Study 109 through 48 weeks are presented in Table 7.



**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

**Table 7 Virologic Outcomes of Study 109 at Week 48<sup>a</sup>**

	<b>FTC+TAF (Administered as GENVOYA) (N=959)</b>	<b>Baseline Regimen (N=477)</b>
<b>HIV-1 RNA &lt;50 copies/mL</b>	97%	93%
Treatment Difference	4.1% (95% CI: 1.6% to 6.7%)	
<b>HIV-1 RNA ≥50 copies/mL<sup>b</sup></b>	1%	1%
<b>No Virologic Data at Week 48 Window</b>	2%	6%
Discontinued Study Drug Due to AE or Death <sup>c</sup>	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL <sup>d</sup>	1%	4%
Missing Data During Window but on Study Drug	0%	< 1%

- Week 48 window was between Day 294 and 377 (inclusive).
- Included patients who had ≥ 50 copies per mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
- Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
- Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

At Week 48, in patients who had received ATRIPLA as their prior treatment regimen, 96% (241/251) of those who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet remained suppressed (HIV-1 RNA < 50 copies per mL) vs. 90% (112/125) of patients those who stayed on ATRIPLA; in patients who had received TRUVADA plus boosted atazanavir, 97% (390/402) of those who switched remained suppressed vs. 92% (183/199) of those who stayed on TRUVADA plus boosted atazanavir; in patients who had received STRIBILD, 98% (301/306) of those patients who switched remained suppressed vs. 97% (149/153) of those who stayed on STRIBILD.

Switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet was superior to staying on a baseline regimen in maintaining HIV-1 RNA < 50 copies per mL.

The mean increase from baseline in CD4+ cell count at Week 48 was 35 cells/mm<sup>3</sup> in patients who switched and 24 cells per mm<sup>3</sup> in those who stayed on their baseline regimen.

**Bone Mineral Density:** In Study 109, changes in BMD from baseline to Week 48 were assessed by DXA. Results are summarized in Table 8.

**Table 8 Measures of Bone Mineral Density in Study 109 (Week 48 analysis)**

	<b>FTC+TAF (Administered as GENVOYA)</b>	<b>Baseline Regimen</b>	<b>Treatment Difference</b>
<b>Hip DXA Analysis</b>	<b>N=869</b>	<b>N=428</b>	
Mean Percent Change in BMD	1.5%	-0.3%	1.81% p < 0.001
Patients with Categorical Change:			
> 3% Decrease in BMD	3%	13%	--
> 3% Increase in BMD	21%	7%	
Patients with No Decrease in BMD	78%	46%	--
<b>Lumbar Spine DXA Analysis</b>	<b>N=881</b>	<b>N=436</b>	
Mean Percent Change in BMD	1.6%	-0.4%	2.0% p < 0.001
Patients with Categorical Change:			
> 3% Decrease in BMD	8%	19%	--
> 3% Increase in BMD	33%	13%	
Patients with No Decrease in BMD	74%	47%	--

**Changes in Renal Laboratory Tests:** There were decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria (urinary RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio), and other measures of proximal renal tubular dysfunction (including fractional excretion of uric acid [FEUA]) in patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet, as compared with increases from baseline in patients who stayed on their FTC+TDF-containing baseline regimen, collectively indicating the reduced impact of TAF on proximal renal tubular function. The median percentage change in UPCR was -21% vs. 10%; in UACR it was -18% vs. 9%; in urine RBP to creatinine ratio it was -33% vs. 18%; and in urine beta-2-microglobulin to creatinine ratio it was -52% vs. 19% (p< 0.001 for all comparisons).

### **Study 1089**

In Study 1089, the efficacy and safety of switching from TRUVADA to DESCOVY while maintaining the third antiretroviral agent was evaluated in a randomised, double-blind study of virologically-suppressed HIV-1 infected adults (N=663). Patients must have been stably suppressed (HIV-1 RNA < 50 copies per mL) on their baseline regimen for at least 6 months. Patients were randomized in a 1:1 ratio to either switch to DESCOVY while maintaining their third agent at baseline (N=333), or stay on their baseline TRUVADA-containing regimen (N=330). Patients had a mean age of 48 years (range 22-79), 85% were male, 75% were White, and 21% were Black. The mean baseline CD4+ cell count was 679 cells per mm<sup>3</sup> (range 79-2201).

Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 46% of patients were receiving TRUVADA in combination with a boosted protease inhibitor and 54% of patients were receiving TRUVADA in combination with an unboosted third agent.

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

Treatment outcomes of Study 1089 through 48 weeks are presented in Table 9.

**Table 9 Virologic Outcomes of Study 1089 at Week 48<sup>a</sup>**

	<b>DESCOVY Containing Regimen (N=333)</b>	<b>Baseline TRUVADA Containing Regimen (N=330)</b>
<b>HIV-1 RNA &lt; 50 copies/mL</b>	94%	93%
Treatment Difference	1.3% (95% CI: -2.5% to 5.1%)	
<b>HIV-1 RNA ≥50 copies/mL<sup>b</sup></b>	< 1%	2%
<b>No Virologic Data at Week 48 Window</b>	5%	5%
Discontinued Study Drug Due to AE or Death <sup>c</sup>	2%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL <sup>d</sup>	3%	5%
Missing Data During Window but on Study Drug	< 1%	0%

- a. Week 48 window was between Day 294 and 377 (inclusive).  
b. Included patients who had  $\geq 50$  copies per mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of  $\geq 50$  copies per mL.  
c. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.  
d. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

At Week 48, in patients who received a boosted protease inhibitor, 92% (142/155) of those who switched from TRUVADA to DESCOVY remained suppressed vs. 93% (140/151) of those who stayed on TRUVADA; in patients who received an unboosted third agent, 97% (172/178) of those who switched from TRUVADA to DESCOVY remained suppressed vs. 93% (167/179) of those who stayed on TRUVADA. Switching to a DESCOVY-containing regimen was non-inferior to staying on a baseline TRUVADA-containing regimen in maintaining HIV-1 RNA < 50 copies per mL. The mean increase from baseline in CD4+ cell count at Week 48 was 20 cells per mm<sup>3</sup> in patients who switched and 21 cells per mm<sup>3</sup> in those who stayed on their baseline TRUVADA-containing regimen.

**Bone Mineral Density:** In Study 1089, changes in BMD from baseline to Week 48 were assessed by DXA. Results are summarized in Table 10.

**Table 10 Measures of Bone Mineral Density in Study 1089 (Week 48 analysis)**

	<b>DESCOVY Containing Regimen</b>	<b>Baseline TRUVADA Containing Regimen</b>	<b>Treatment Difference</b>
<b>Hip DXA Analysis</b>	<b>N=300</b>	<b>N=303</b>	

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

	<b>DESCOVY Containing Regimen</b>	<b>Baseline TRUVADA Containing Regimen</b>	<b>Treatment Difference</b>
Mean Percent Change in BMD	1.1%	-0.2%	1.29% p < 0.001
Patients with Categorical Change:			
> 3% Decrease in BMD	5%	13%	--
> 3% Increase in BMD	17%	9%	
Patients with No Decrease in BMD	70%	44%	--
<b>Lumbar Spine DXA Analysis</b>	<b>N=300</b>	<b>N=306</b>	
Mean Percent Change in BMD	1.5%	-0.2%	1.74% p < 0.001
Patients with Categorical Change:			
> 3% Decrease in BMD	6%	17%	--
> 3% Increase in BMD	30%	14%	
Patients with No Decrease in BMD	69%	44%	--

**Changes in Renal Laboratory Tests:** There were decreases from baseline in proteinuria, albuminuria, and tubular proteinuria in patients receiving a regimen containing DESCOVY, as compared with increases in patients who stayed on a regimen containing TRUVADA at baseline, collectively indicating the reduced impact of TAF on proximal renal tubular function. The median percentage change in UPCR was -15% vs. -8%; in UACR it was -8% vs. 12%; in urine RBP to creatinine ratio it was -16% vs. 18%; and in urine beta-2-microglobulin to creatinine ratio it was -40% vs. 22% (p < 0.001 for all comparisons).

### **HIV-1 Infected Patients with Renal Impairment**

In Study 112, the efficacy and safety of FTC+TAF were evaluated in an open-label clinical trial in which 242 HIV-1 infected patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method between 30 to 69 mL per minute) switched to FTC+TDF in combination with EVG+COBI as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies per mL) for at least 6 months before switching.

The mean age was 58 years (range 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients identified as Hispanic/Latino. At baseline, median eGFR was 56 mL per minute, and 33% of patients had an eGFR of 30 to 49 mL per minute. The mean baseline CD4+ cell count was 664 cells/mm<sup>3</sup> (range 126-1813).

At Week 24, 95% (230/242 patients) maintained HIV-1 RNA < 50 copies per mL after switching to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. At Week 48, 93.0% (225/242 patients) maintained HIV-1 RNA < 50 copies per mL after switching to FTC+TAF given with EVG+COBI. At Week 72, based on missing = failure analysis, 93.4% (226/242) maintained HIV-1 RNA < 50 copies per mL after switching to FTC+TAF given with EVG+COBI and 3 patients had HIV-1 RNA ≥ 50 copies per mL at Week 72.

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

In a substudy (N=32), patients had no change from baseline in their actual glomerular filtration rate at Week 24, as measured by iohexol clearance.

Changes from baseline in renal laboratory tests in Study 112 are summarized in Table 11.

**Table 11 Change from Baseline in Renal Laboratory Tests at Week 72 in Virologically Suppressed Patients with Renal Impairment who Switched to FTC+TAF (Administered as GENVOYA in Study 112 (Week 72 analysis))**

	<b>FTC+TAF (Administered as GENVOYA) N=242</b>
Serum Creatinine (mg/dL) <sup>a</sup>	-0.02 ± 0.26
Improvement in Proteinuria by Urine Dipstick <sup>b</sup>	55/74 (74%)
Urine Protein to Creatinine Ratio [UPCR] <sup>c</sup>	-36.1%
Urine Albumin to Creatinine Ratio [UACR] <sup>c</sup>	-44.1%
Urine RBP to Creatinine Ratio <sup>c</sup>	-68.9%
Urine Beta-2-Microglobulin to Creatinine Ratio <sup>c</sup>	-76.5%

a. Mean change ± SD.

b. An improvement of at least 1 toxicity grade from baseline.

c. Median percent change.

Multiple assessments of renal function indicate that improvements in renal function occur as early as 1 week after the switch to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet and persist through 72 weeks. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% at baseline to 18% at Week 72 and 49% at baseline to 29% at Week 72, respectively. Other renal assessments, including fractional excretion of uric acid, serum cystatin C, and serum phosphorus showed small changes from baseline through Week 72.

In patients whose prior antiretroviral regimen did not include TDF (N=84), mean change from baseline in serum creatinine at Week 72 was 0.01 ± 0.21 mg/dL; 50% of patients had an improvement in proteinuria as measured by urine dipstick; and median percent change in UPCR and UACR were 1% and -19%, respectively. Median percent change in urine RBP to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio at Week 72 were 21% and -16%, respectively.

In virologically suppressed patients with renal impairment who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet, mean percentage increases from baseline at Week 72 were observed in hip and spine BMD. Assessment of BMD using a threshold of 3% for changes from baseline revealed higher percentages of patients had increases versus decreases from baseline in BMD at both hip and spine.

## **Paediatric Patients**

In Study 106, the efficacy, safety, and pharmacokinetics of FTC+TAF were evaluated in an open-label trial, in which HIV-1-infected treatment-naïve adolescents received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. Fifty patients had a mean age of 15 years (range: 12 to 17), were 44% male, 12% Asian, and 88% black. At baseline, mean plasma HIV-1 RNA was 4.6 log<sub>10</sub> copies per mL, median CD4+ cell count was 456 cells/mm<sup>3</sup> (range: 95 to 1110), and median CD4+% was 23% (range: 7% to 45%). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies per mL.

At 48 weeks, 92% achieved HIV-1 RNA < 50 copies per mL, similar to response rates in trials of treatment naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm<sup>3</sup>. Three patients had virologic failure by snapshot at Week 48; no emergent resistance to FTC+TAF was detected through Week 48.

Mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for total body less head.

## **INDICATIONS**

DESCOVY is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of DESCOVY (see PHARMACOLOGY).

DESCOVY is not for use in Pre-Exposure Prophylaxis (PrEP).

## **CONTRAINDICATIONS**

DESCOVY is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.

Please see Table 12 for Established and Other Potentially Significant Drug Interactions. In addition, prescribing information for any drug coadministered with DESCOVY should be consulted to exclude significant interaction or contraindication.

## **PRECAUTIONS**

### **General**

Patients receiving DESCOVY or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of HIV transmission, a residual risk cannot be excluded. Appropriate precautions must continue to be used. Patients should also be informed that DESCOVY is not a cure for HIV infection.



### **Lactic Acidosis/Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with DESCOVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

### **HIV and Hepatitis B Virus (HBV) Co-infection**

The safety and efficacy of DESCOVY have not been established in patients co-infected with HBV and HIV-1. Individuals should be tested for the presence of hepatitis B virus (HBV) before initiating DESCOVY. Discontinuation of DESCOVY therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TAF components of DESCOVY. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping DESCOVY treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

### **Use with Other Antiretroviral Products**

DESCOVY should not be coadministered with products containing any of the same components, TAF or FTC; or with products containing lamivudine or tenofovir disoproxil fumarate. DESCOVY should not be administered with adefovir dipivoxil.

Data support use of DESCOVY with HIV-1 protease inhibitors atazanavir, darunavir and lopinavir (see Table 12). For treatment of HIV and Hepatitis C co-infection, DESCOVY should not be used in conjunction with protease inhibitors that are inhibitors of cathepsin A (such as anti-Hepatitis C agents telaprevir and boceprevir) due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of TAF.

### **Lipodystrophy**

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

### **Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FTC, a component of DESCOVY. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

### **Impairment of Fertility**

No reproductive toxicity studies have been conducted with FTC and TAF in combination.

**Emtricitabine:** Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

**Tenofovir Alafenamide:** There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

### **Use in Pregnancy**

Pregnancy Category B3.

There are no adequate and well controlled clinical studies of DESCOVY or its components in pregnant women. Because animal reproductive studies are not always predictive of human response, DESCOVY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Emtricitabine:** No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse fetal effects.

**Tenofovir Alafenamide:** Embryofetal development studies performed in rats and rabbits revealed no evidence of embryoletality, fetotoxicity or teratogenicity due to TAF. The embryo-fetal NOAELs in rats and rabbits occurred at TAF exposures (AUC) similar to and 53 times higher than, respectively, the exposure in humans at the recommended daily dose.

### **Use in Lactation**

In animal studies it has been shown that tenofovir is secreted into milk. It is not known whether TAF is secreted in human milk. In humans, samples of breast milk obtained from five HIV-1 infected mothers given TRUVADA (TDF/FTC) show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC<sub>50</sub> but 3 to 12 times lower than the C<sub>min</sub> achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown. Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with TAF are unknown.

Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving DESCOVY.

### **Use in Children**

The safety, virologic, and immunologic responses in patients who received DESCOVY were evaluated through Week 24 in 23 treatment-naïve, HIV-1 infected patients aged 12 to less than 18 years in an open-label trial, Study 106 (see CLINICAL TRIALS).

Pharmacokinetic parameters, evaluated in 24 patients weighing  $\geq 35$  kg were similar to adults receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet (see Pharmacokinetics). See DOSAGE AND ADMINISTRATION for dosing recommendations for paediatric patients aged 12 years and older and weighing at least 35 kg. No data are available on which to make a dose recommendation for pediatric patients younger than 12 years or weighing less than 35 kg. The safety profile in 23 adolescent patients was similar to that in adults (see ADVERSE EVENTS).

### **Use in the Elderly**

In clinical trials, 80 of the 97 patients enrolled aged 65 years and over received FTC and TAF given with EVG and COBI as a fixed-dose combination tablet. No differences in safety or efficacy have been observed between elderly patients and those between 12 and less than 65 years of age.

### **Renal Impairment**

The safety, virologic, and immunologic responses of FTC+TAF was evaluated through 24 weeks in an open-label clinical study (Study 0112) in which 248 HIV-1 infected adult patients who were either treatment-naïve (N=6) or virologically suppressed (N=242) with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30 - 69 mL per min) received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. The safety profile of FTC+TAF in patients with mild to moderate renal impairment was similar to safety data that from patients with normal renal function.

No dose adjustment of DESCOVY is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL per min.

DESCOVY should not be initiated in patients with estimated creatinine clearance below 30 mL per minute as there are no data available regarding the use of DESCOVY in this

population (see DOSAGE AND ADMINISTRATION). No data are available to make dose recommendations in pediatric patients with renal impairment.

Estimated creatinine clearance, urine glucose, and urine protein should be measured prior to starting DESCOVY, and should be monitored routinely during treatment. In addition, serum phosphate should be routinely measured in patients with chronic kidney disease.

### **Hepatic Impairment**

No dose adjustment of DESCOVY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see CLINICAL TRIALS and Pharmacokinetics).

### **Animal Toxicology**

#### **Genotoxicity**

No genotoxicity studies have been conducted with FTC and TAF in combination.

#### ***Emtricitabine***

FTC was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

#### ***Tenofovir Alafenamide***

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

#### **Carcinogenicity**

No carcinogenicity studies have been conducted with FTC and TAF in combination.

***Emtricitabine:*** In long-term oral carcinogenicity studies conducted with FTC, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

***Tenofovir Alafenamide:*** Because there is a lower tenofovir exposure in rats and mice after TAF compared to TDF, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose.

## **Drug Interactions and Other Forms of Interactions**

### **General**

As DESCOVY contains FTC any interactions that have been identified with FTC individually may occur with DESCOVY.

### **Effects of concomitant drugs on the Pharmacokinetics of DESCOVY**

TAF, a component of DESCOVY, is transported by P-glycoprotein (P-gp). Drugs that strongly affect P-gp activity may lead to changes in TAF absorption (see Table 12). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of DESCOVY and development of resistance. Coadministration of DESCOVY with other drugs that inhibit P-gp may increase the absorption and plasma concentration of TAF.

### **Established and Other Potentially Significant Interactions**

Drug interaction information for DESCOVY with potential concomitant drugs is summarized in Table 12. The drug interactions described are based on studies conducted with DESCOVY or the components of DESCOVY (FTC and TAF) as individual agents, or are potential drug interactions that may occur with DESCOVY.

The table is not all-inclusive (see CONTRAINDICATIONS).

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

**Table 12 Established and Other Potentially Significant Drug Interactions**

<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>Antiretroviral Agents: Protease Inhibitors (PI)</b>		
Atazanavir/cobicistat	↑ tenofovir alafenamide	TAF exposure is expected to increase when atazanavir/cobicistat is used in combination with DESCOPY. The recommended dose of DESCOPY is 200/10 mg once daily.
Atazanavir/ritonavir <sup>c</sup>	↑ tenofovir alafenamide	TAF exposure is increased when atazanavir/ritonavir is used in combination with DESCOPY. The recommended dose of DESCOPY is 200/10 mg once daily.
Darunavir/cobicistat <sup>c</sup>	↔ tenofovir alafenamide ↑ tenofovir	Tenofovir exposure is increased when darunavir /cobicistat is used in combination with DESCOPY. The recommended dose of DESCOPY is 200/10 mg once daily.
Darunavir/ritonavir <sup>c</sup>	↔ tenofovir alafenamide ↑ tenofovir	Tenofovir exposure is increased when darunavir/ritonavir is used in combination with DESCOPY. The recommended dose of DESCOPY is 200/10 mg once daily.
Lopinavir/ritonavir <sup>c</sup>	↑ tenofovir alafenamide	TAF exposure is increased when lopinavir/ritonavir is used in combination with DESCOPY. The recommended dose of DESCOPY is 200/10 mg once daily.
Tipranavir/ritonavir	↓ tenofovir alafenamide	Tenofovir alafenamide exposure may decrease when tipranavir/ritonavir is used in combination with DESCOPY. There are no data available to make dosing recommendations. Coadministration with DESCOPY is not recommended.
Other Protease Inhibitors	Effect is unknown	There are no data available to make dosing recommendations for coadministration with other protease inhibitors.
<b>Other Agents</b>		
<b>Anticonvulsants:</b> carbamazepine oxcarbazepine phenobarbital phenytoin	↓ tenofovir alafenamide	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
<b>Antifungals:</b> itraconazole ketoconazole	↑ tenofovir alafenamide	Coadministration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of TAF. No dose adjustment is required.



**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>Antimycobacterial:</b> rifabutin  rifampicin  rifapentine	↓ tenofovir alafenamide	Coadministration of rifampicin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of DESCOVY with rifabutin, rifampicin, or rifapentine is not recommended.
<b>Herbal Products:</b> St. John's wort (Hypericum perforatum)	↓ tenofovir alafenamide	Coadministration of St. John's wort, a P-gp inducer, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance.  Coadministration of DESCOVY with St. John's wort is not recommended.

- a. This table is not all inclusive.  
b. ↑ = increase, ↓ = decrease, ↔ = no effect  
c. Indicates that a drug-drug interaction study was not conducted.

### **Drugs Without Clinically Significant Interactions with DESCOVY**

Based on drug interaction studies conducted with the components of DESCOVY and the following antiretroviral agents, no clinically significant drug interactions were observed with dolutegravir, efavirenz, ledipasvir/sofosbuvir, or rilpivirine. No clinically significant drug interactions are expected when DESCOVY is combined with maraviroc, nevirapine, or raltegravir.

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions were observed when DESCOVY was combined with midazolam or sertraline. No clinically significant drug interactions are expected when DESCOVY is combined with buprenorphine, methadone, naloxone, norbuprenorphine, or norgestimate/ethinyl estradiol.

### **Effects on ability to drive and use machines**

No studies on the effects of DESCOVY on the ability to drive and use machines have been performed.

### **ADVERSE EFFECTS**

As DESCOVY contains FTC, adverse reactions associated with FTC may be expected to occur with the fixed combination tablet.

For additional safety information about EMTRIVA (FTC), in combination with other antiretroviral agents, consult the Product Information.

## CLINICAL TRIALS

The safety of DESCOVY is based on studies of FTC and TAF when given with EVG+COBI as the fixed-dose combination tablet GENVOYA.

### Experience from Clinical Studies in Treatment-Naïve Patients

Assessment of adverse reactions is based on pooled data from two 48-week controlled clinical studies (Study 0104 and Study 0111) in which 1733 treatment-naïve patients received FTC+TAF (N=866) or FTC+TDF (N=867), both given with EVG+COBI as a fixed-dose combination tablet.

The most common adverse reaction (all Grades) and reported in  $\geq 10\%$  of patients in the FTC+TAF group was nausea. The proportion of subjects who discontinued treatment with FTC+TAF or FTC+TDF due to adverse events, regardless of severity, was 0.9% and 1.5%, respectively. Table 13 displays the frequency of adverse reactions (Grades 2-4) greater than or equal to 1%.

**Table 13 Adverse Drug Reactions<sup>a</sup> (Grades 2-4) Reported in  $\geq 1\%$  of HIV-1 Infected Treatment-Naïve Adults in Any Treatment Arm in Studies 104 and 111 (Week 96 analysis)**

	<b>FTC+TAF (Administered as GENVOYA) N=866</b>	<b>FTC+TDF (Administered as STRIBILD) N=867</b>
<b>GASTROINTESTINAL DISORDERS</b>		
Diarrhoea	1%	< 1%
Nausea	< 1%	1%
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>		
Fatigue	1%	< 1%
<b>NERVOUS SYSTEM DISORDERS</b>		
Headache	1%	< 1%

a. Frequencies of adverse reactions are based on Grades 2-4 adverse events attributed to study drugs by the investigator.

In addition to the adverse reactions presented in Table 11, abdominal pain, dyspepsia, flatulence, rash, and vomiting occurred at a frequency of < 1% and/or at severity of Grade 1 in the FTC+TAF group.

### Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving FTC+TAF given with EVG+COBI as a fixed-dose combination tablet in Studies 104 and 111 are presented in Table 14.

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

**Table 14: Laboratory Abnormalities (Grades 3-4) Reported in  $\geq$  2% of Patients Receiving FTC+TAF (Administered as GENVOYA in Studies 104 and 111 (Week 96 analysis))**

	<b>FTC+TAF (Administered as GENVOYA) N=866</b>	<b>FTC+TDF (Administered as STRIBILD) N=867</b>
<b>Laboratory Parameter Abnormality<sup>a</sup></b>		
Creatine Kinase ( $\geq$ 10.0 x ULN)	9%	7%
LDL-cholesterol (fasted) ( $>$ 190 mg/dL)	8%	4%
Total cholesterol (fasted) ( $>$ 300 mg/dL)	3%	2%
AST ( $>$ 5.0 x ULN)	2%	2%
Amylase ( $>$ 2.0 x ULN)	2%	4%
Urine RBC (Hematuria) ( $>$ 75 RBC/HPF)	3%	3%

a. Frequencies are based on treatment-emergent laboratory abnormalities.

### **Serum Lipids**

In the clinical trials of FTC+TAF and FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet, a similar percentage of patients receiving FTC+TAF and FTC+TDF were on lipid lowering agents at baseline (4% and 5%, respectively). While receiving study drug through Week 48, an additional 4% of FTC+TAF patients were started on lipid lowering agents, compared to 3% of FTC+TDF patients.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 15.

**Table 15 Lipid Values, Mean Change from Baseline, Reported in Patients FTC+TAF (Administered as GENVOYA) or FTC+TAF (Administered as STRIBILD) in Studies 104 and 111<sup>a</sup> (Week 96 analysis)**

	FTC+TAF (Administered as GENVOYA) N=866		FTC+TAF (Administered as STRIBILD) N=867	
	Baseline	Week 96	Baseline	Week 96
	mg/dL	Change <sup>b</sup>	mg/dL	Change <sup>b</sup>
Total Cholesterol (fasted)	162 [N=692]	+31 [N=692]	166 [N=679]	+14 [N=679]
HDL-cholesterol (fasted)	46 [N=692]	+7 [N=692]	46 [N=679]	+4 [N=679]
LDL-cholesterol (fasted)	103 [N=688]	+18 [N=688]	107 [N=680]	+7 [N=680]
Triglycerides (fasted)	113 [N=692]	+31 [N=692]	115 [N=679]	13 [N=679]
Total Cholesterol to HDL ratio	3.7 [N=692]	0.2 [N=692]	3.9 [N=679]	0 [N=679]

a Excludes subjects who received lipid lowering agents during the treatment period.

b The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 96 values.

### Experience from Clinical Studies in Virologically Suppressed Patients

No new adverse reactions to DESCOVY were identified through Week 48 in an open-label clinical study (Study 109) of virologically suppressed patients who switched treatment from a TDF-containing combination regimen to FTC+TAF given with EVG+COBI as a fixed-dose combination tablet (N=959).

No new adverse reactions to DESCOVY were identified through Week 48 in a randomised double-blind clinical study (GS-US-311-1089) of virologically suppressed patients who switched treatment from a TRUVADA-containing regimen to a DESCOVY-containing regimen (N=333).

### Experience from Clinical Studies in Patients with Renal Impairment

The safety of DESCOVY was evaluated through 72 weeks in an open-label clinical study (Study 0112) in which 248 HIV-1 infected patients who were either treatment-naïve (N=6) or virologically suppressed (N=242) with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 30-69 mL per min) received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. The safety profile of FTC+TAF in patients with mild to moderate renal impairment was similar to that from patients with normal renal function (see CLINICAL TRIALS).

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

In 84 renally impaired patients who switched to FTC+TAF given with EVG+COBI as a fixed-dose combination in Study 112 from antiviral regimens not containing TDF, mean change from baseline in fasting lipid laboratory tests at Week 72 were -9 mg/dL in total cholesterol, -10 mg/dL in LDL-cholesterol, -4 mg/dL in HDL cholesterol, and -5 mg/dL in triglycerides.

### Experience from Clinical Studies in Paediatric Patients

The safety of DESCOVY was evaluated through 48 weeks in an open-label clinical study (Study 106) in which HIV-1 infected, treatment-naïve paediatric patients aged 12 to < 18 years received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. The safety profile of FTC+TAF in 50 adolescent patients was similar to that in adults.

### DOSAGE AND ADMINISTRATION

In adults and adolescent patients aged 12 years and older and weighing  $\geq 35$  kg DESCOVY is taken orally once daily with or without food.

The recommended dose of DESCOVY is 200/25 mg.

If DESCOVY is used in combination with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat, the recommended dose of DESCOVY is 200/10 mg (see Table 16).

**Table 16 Dose of DESCOVY according to third agent in the HIV treatment regimen**

Dose of DESCOVY	Third agent in HIV treatment regimen <sup>1</sup>
Descovy 200/10 mg once daily	Atazanavir with ritonavir or cobicistat Darunavir with ritonavir or cobicistat <sup>2</sup> Lopinavir with ritonavir
Descovy 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

<sup>1</sup> See Drug Interactions and Other Forms of Interactions

<sup>2</sup> Descovy 200/10 mg in combination with darunavir 800 mg and cobicistat 150 mg, administered as a fixed-dose combination tablet, was studied in treatment-naïve patients

See also Drug Interactions and Other Forms of Interactions. For specific dosing recommendations for coadministered antiretroviral agents, refer to their respective Product Information.

No data are available on which to make a dose recommendation for pediatric patients younger than 12 years or weighing less than 35 kg.

*Elderly:* No dose adjustment is required for elderly patients. In clinical trials of 80 of the 97 patients enrolled aged 65 years and over received FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. No differences in safety or efficacy have been observed between elderly patients and those between 12 and less than 65 years of age.

**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

*Renal impairment:* No dose adjustment of DESCOVY is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL per minute.

DESCOVY should not be initiated in patients with estimated creatinine clearance below 30 mL per minute as there are no data available regarding the use of DESCOVY in this population.

No data are available to make dose recommendations in pediatric patients with renal impairment.

*Hepatic Impairment:* No dose adjustment of DESCOVY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see Pharmacological Properties: Pharmacokinetics in Special Populations).

## OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with DESCOVY consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

*Emtricitabine:* Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL per min and a dialysate flow rate of 600 mL per min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

*Tenofovir Alafenamide:* Limited clinical experience is available at doses higher than the therapeutic dose of TAF. A single suprathreshold dose of 125 mg TAF was administered to 48 healthy subjects, no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

## PRESENTATION AND STORAGE CONDITIONS

DESCOVY is available as tablets.

DESCOVY 200/25 mg tablets contain 200 mg of FTC and TAF fumarate equivalent to 25 mg tenofovir alafenamide. The tablets are film-coated, rectangular shaped and blue in colour. Each tablet is debossed with 'GSI' on one side and the number "225" on the other side.



**Attachment 1: Product information for AusPAR Descovy Emtricitabine/Tenofovir alafenamide (as fumarate) Gilead Sciences Pty Ltd**  
**PM-2015-01283-1-3 Final 20 December 2016. This Product Information was approved at the time this AusPAR was published.**

DESCOVY 200/10 mg tablets contain 200 mg of FTC and TAF fumarate equivalent to 10 mg tenofovir alafenamide. The tablets are film-coated, rectangular shaped and gray in colour. Each tablet is debossed with 'GSI' on one side and the number "210" on the other side.

DESCOVY is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a silica gel desiccant, polyester coil and is closed with a child resistant closure.

DESCOVY should be stored below 30 °C.

#### **NAME AND ADDRESS OF THE SPONSOR**

Gilead Sciences Pty Ltd  
Level 6, 417 St Kilda Road  
Melbourne, Victoria 3004

#### **POISON SCHEDULE OF THE DRUG**

S4

#### **DATE OF INCLUSION ON ARTG:**

1 July 2016

DESCOVY, EMTRIVA GENVOYA, , GILEAD, GSI, STRIBILD and TRUVADA are registered trademarks of Gilead Sciences, Inc., or its related companies. ATRIPLA is a registered trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. All other trademarks referenced herein are the property of their respective owner