

## Product Information

### STRIBILD™ (tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat) tablets

#### NAME OF THE MEDICINE

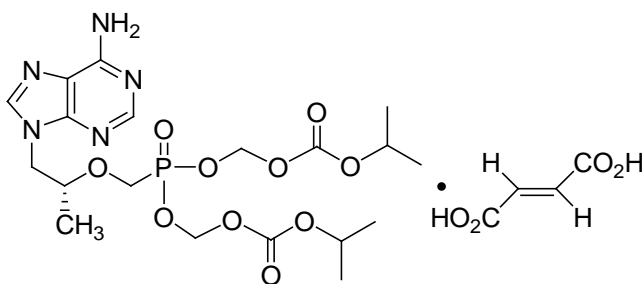
STRIBILD (tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat) tablets.

The active substances in STRIBILD tablets are tenofovir disoproxil fumarate (tenofovir DF), emtricitabine, elvitegravir and cobicistat.

VIREAD® is the brand name for tenofovir DF, which is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. EMTRIVA® is the brand name for emtricitabine (FTC), a synthetic nucleoside analog of cytidine. Tenofovir DF and emtricitabine exhibit activity against HIV-1 reverse transcriptase (RT). Tenofovir DF and emtricitabine are the components of TRUVADA®. Elvitegravir is a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor. Cobicistat is a mechanism-based inhibitor of cytochrome P-450 (CYP) enzymes of the CYP3A family.

#### DESCRIPTION

**Tenofovir disoproxil fumarate:** Tenofovir DF is a fumaric acid salt of the *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2-[[bis[[isopropoxycarbonyloxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of C<sub>19</sub>H<sub>30</sub>N<sub>5</sub>O<sub>10</sub>P · C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> and a molecular weight of 635.52. It has the following structural formula:



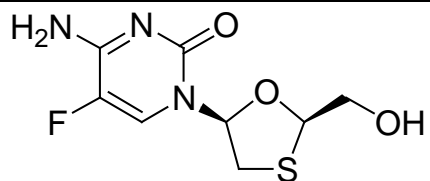
CAS registry number: 202138-50-9

Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (*log p*) for tenofovir disoproxil is 1.25 and the pKa is 3.75.

**Emtricitabine:** The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine 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 247.24. It has the following structural formula:

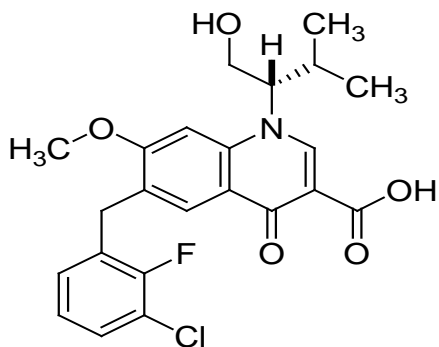
**Attachment 1: Product information for AusPAR Stribild; tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat; Gilead Sciences Pty Ltd; PM-2011-03533-3-2. Date of Finalisation 5 August 2013. This Product Information was approved at the time this AusPAR was published.**



CAS registry number: 143491-57-0

Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient ( $\log p$ ) for emtricitabine is -0.43 and the pKa is 2.65.

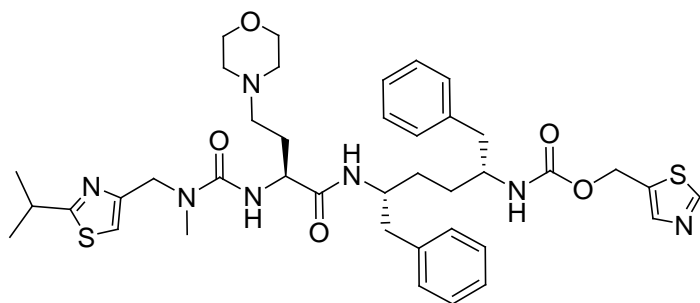
**Elvitegravir:** The chemical name of elvitegravir is 3-quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)-methyl]-1,4-dihydro-1-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-. It has a molecular formula of C<sub>23</sub>H<sub>23</sub>ClFNO<sub>5</sub> and a molecular weight of 447.9. It has the following structural formula. It has the following structural formula:



CAS registry number: 697761-98-1

Elvitegravir is a white to pale yellow solid with a solubility of less than 0.5 µg/mL in water at 20 °C. The partition coefficient ( $\log p$ ) for elvitegravir is 4.5 and the pKa is 6.6.

**Cobicistat:** the chemical name for cobicistat is 1,3-Thiazol-5-ylmethyl [(2R,5R)-5-{[(2S)-2-[(methyl{2-(propan-2-yl)-1,3-thiazol-4-yl}]methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate. It has a molecular formula of C<sub>40</sub>H<sub>53</sub>N<sub>7</sub>O<sub>5</sub>S<sub>2</sub> and a molecular weight of 776.0. It has the following structural formula:



CAS registry number: 1004316-88-4

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Cobicistat is a white to pale yellow solid with a solubility of 0.08 mg/mL in water with pH 6.8 phosphate buffer at 25 °C. The partition coefficient ( $\log p$ ) for cobicistat is 4.3 and the pKa is 6.4.

**STRIBILD** tablets contain the following ingredients as excipients:

*Tablet core:* lactose, cellulose-microcrystalline (E460), silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate (E572), sodium lauryl sulphate. *Film-coating:* indigo carmine (FD&C blue #2) aluminum lake, macrogol 3350, polyvinyl alcohol, talc, titanium dioxide (E171), yellow iron oxide.

Each STRIBILD tablet is capsule shaped, film-coated and green in colour. Each tablet is debossed with 'GSI' on one side and the number "1" surrounded by a square box ( 1 ) 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: J05AR09.

### Mechanism of action

STRIBILD is a fixed-dose combination of antiviral drugs tenofovir DF, emtricitabine and elvitegravir, boosted by the pharmacokinetic enhancer cobicistat.

**Tenofovir disoproxil fumarate:** is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$ , and mitochondrial DNA polymerase  $\gamma$ .

**Emtricitabine:** a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$ ,  $\epsilon$  and mitochondrial DNA polymerase  $\gamma$ .

**Elvitegravir:** Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II.

**Cobicistat:** Cobicistat is a selective mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5). Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

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

***Tenofovir disoproxil fumarate, emtricitabine and elvitegravir/cobicistat:*** The triple combination of tenofovir, emtricitabine, and elvitegravir demonstrated synergistic antiviral activity in cell culture. Antiviral synergy was maintained for tenofovir, emtricitabine, and elvitegravir when tested in the presence of cobicistat.

***Tenofovir disoproxil fumarate:*** The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC<sub>50</sub> (50% inhibitory concentration) values for tenofovir were in the range of 0.04 to 8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC<sub>50</sub> values ranged from 0.5 to 2.2 µM). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

***Emtricitabine:*** The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC<sub>50</sub> value for emtricitabine was in the range of 0.0013 to 0.64 µM (0.0003 to 0.158 µg/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC<sub>50</sub> values ranged from 0.007 to 0.075 nM) and showed strain specific activity against HIV-2 (IC<sub>50</sub> values ranged from 0.007 to 1.5 nM).

***Elvitegravir:*** The antiviral activity of elvitegravir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cells, monocyte/macrophage cells, and peripheral blood lymphocytes and the 50% effective concentration (EC<sub>50</sub>) values were in the range of 0.02 to 1.7 nM. Elvitegravir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC<sub>50</sub> values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC<sub>50</sub> of 0.53 nM). The antiviral activity of elvitegravir with antiretroviral drugs in two-drug combination studies was additive to synergistic when combined with NRTIs (abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, or AZT); NNRTIs (efavirenz, etravirine, or nevirapine); protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir); the integrase strand transfer inhibitor raltegravir; the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist, maraviroc. No antagonism was observed for these combinations.

Elvitegravir did not show inhibition of replication of HBV or HCV *in vitro*.

***Cobicistat:*** Cobicistat has no detectable antiviral activity against HIV-1, HBV or HCV and does not antagonise the antiviral effects of elvitegravir, emtricitabine, or tenofovir.

## **Drug Resistance**

### **In Cell Culture:**

***Tenofovir disoproxil fumarate:*** HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

***Emtricitabine:*** Emtricitabine-resistant isolates of HIV have been selected *in vitro*. 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).

***Elvitegravir:*** HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was most commonly associated with the primary integrase substitutions T66I, E92Q, and Q148R. Additional integrase substitutions observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K.

Elvitegravir showed cross-resistance *in vitro* to the raltegravir selected mutations T66A/K, Q148H/K, and N155H.

***Cobicistat:*** No *in vitro* resistance can be demonstrated with cobicistat due to its lack of antiviral activity.

### **In Clinical Studies:**

#### ***Tenofovir disoproxil fumarate, emtricitabine and elvitegravir/cobicistat:***

In a pooled analysis of antiretroviral-naïve patients receiving STRIBILD in clinical trials GS-US-236-0102 and GS-US-236-0103, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed virologic failure or had HIV-1 RNA > 400 copies/mL at Week 48 or at the time of early study drug discontinuation. As of Week 48, the development of one or more primary elvitegravir, emtricitabine, or tenofovir resistance-associated mutations was observed in 13 of the 25 patients with evaluable genotypic data from paired baseline and STRIBILD treatment-failure isolates (1.9%, 13/701 patients). The most common mutations that emerged were M184V/I and K65R in reverse transcriptase; and T66I, E92Q, Q148R, and N155H in integrase. Other mutations in integrase that occurred in addition to a primary INSTI resistance substitution each in single cases were H51Y, L68V, G140C, S153A and E157Q. Most patients who developed resistance mutations to elvitegravir developed resistance mutations to both emtricitabine and elvitegravir. In phenotypic analyses of patients in the resistance analysis population, 11/25 (44%) patients had HIV-1 isolates with reduced susceptibility to elvitegravir, 12/25 (48%) had reduced susceptibility to emtricitabine, and 2/25 (8%) had reduced susceptibility to tenofovir.

#### **Cross-resistance:**

***Tenofovir disoproxil fumarate, emtricitabine, elvitegravir / cobicistat:*** No significant cross-resistance has been demonstrated for elvitegravir-resistant HIV-1 isolates and emtricitabine or tenofovir, or for emtricitabine- or tenofovir-resistant isolates and elvitegravir. Substantial cross-resistance was observed between elvitegravir-resistant HIV-1 isolates and raltegravir, and

between emtricitabine-resistant isolates and lamivudine. These patient isolates remained susceptible to PIs, NNRTIs, and most other NRTIs.

**Tenofovir disoproxil fumarate:** The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir or didanosine or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and 3TC. Therefore, cross-resistance among these drugs may occur in patients whose virus harbours the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir DF. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

**Emtricitabine:** Emtricitabine-resistant isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, AZT and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine and tenofovir demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT (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.

**Elvitegravir:** Elvitegravir-resistant viruses show varying degrees of cross-resistance to the integrase strand transfer inhibitor raltegravir depending on the type and number of mutations. Viruses expressing the T66I/A mutations maintain susceptibility to raltegravir, while most other patterns showed reduced susceptibility to raltegravir.

## **Pharmacodynamics**

### **Effects on Electrocardiogram**

The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult subjects. Cobicistat did not prolong QTcF interval at exposures 2- and 4-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around  $C_{max}$ , 3 to 5 hours after dosing with 250 mg of cobicistat. This finding was not considered to be clinically significant.

In a thorough QT/QTc study in 126 healthy subjects, elvitegravir at therapeutic or supratherapeutic doses approximately 2 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

### **Pharmacokinetics**

**Tenofovir disoproxil fumarate, emtricitabine and elvitegravir/cobicistat:** Following oral administration of STRIBILD with food in healthy subjects, peak plasma concentrations were observed 4.0 to 4.5 hours post-dose for elvitegravir and cobicistat, 2.5 hours post-dose for emtricitabine, and 3 hours for tenofovir following the rapid conversion of tenofovir DF. The steady-state mean  $C_{max}$ ,  $AUC_{tau}$ , and  $C_{trough}$  (mean  $\pm$  SD) following multiple doses of STRIBILD in HIV-1 infected subjects, respectively, were  $1.7 \pm 0.39$   $\mu\text{g/mL}$ ,  $23 \pm 7.5$   $\mu\text{g}\cdot\text{hr/mL}$ , and  $0.45 \pm 0.26$   $\mu\text{g/mL}$  for elvitegravir, which provides inhibitory quotient of  $\sim 10$  (ratio of  $C_{trough}$ : protein



binding-adjusted IC<sub>95</sub> for wild-type HIV-1 virus). Corresponding steady-state mean C<sub>max</sub>, AUC<sub>tau</sub>, and C<sub>trough</sub> (mean ± SD) were 1.1 ± 0.40 µg/mL, 8.3 ± 3.8 µg•hr/mL, and 0.05 ± 1.3 µg/mL for cobicistat, 1.9 ± 0.5 µg/mL, 13 ± 4.5 µg•hr/mL, and 0.14 ± 0.25 µg/mL for emtricitabine, and 0.45 ± 0.16 µg/mL, 4.4 ± 2.2 µg•hr/mL, and 0.1 ± 0.08 µg/mL for tenofovir.

**Tenofovir disoproxil fumarate:** The pharmacokinetic properties of tenofovir DF are summarized in Table 1. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 to 25 µg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.

**Emtricitabine:** The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 µg/mL. Following administration of radiolabelled emtricitabine 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. Emtricitabine 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.

**Table 1. Single Dose Pharmacokinetic Parameters for Tenofovir and Emtricitabine in Adults<sup>1</sup>**

	Tenofovir	Emtricitabine
Fasted Oral Bioavailability (%)	25	93
Plasma Terminal Elimination Half-Life (hr)	17	10
C <sub>max</sub> (µg/mL)	0.30 ± 0.09	1.8 ± 0.7 <sup>2</sup>
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1 <sup>2</sup>
CL/F (mL/min)	1043 ± 115	302 ± 94
CL <sub>renal</sub> (mL/min)	243 ± 33	213 ± 89

1. Data presented as mean values.
2. Data presented as steady state values.

**Elvitegravir:** Elvitegravir is 98-99% bound to human plasma proteins and binding is independent of drug concentration over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio was 1.37. Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of boosted [<sup>14</sup>C]elvitegravir, elvitegravir was the predominant species in plasma, representing ~ 94% of the circulating radioactivity. Aromatic and aliphatic hydroxylation or glucuronidation metabolites are present in very low levels, display considerably lower anti-HIV activity and do not contribute to the overall antiviral activity of elvitegravir. 94.8% of the dose was recovered in feces, consistent with the hepatobiliary excretion of elvitegravir; 6.7% of the administered dose was recovered in urine as unchanged elvitegravir. The median terminal plasma half-life of elvitegravir following administration of STRIBILD is approximately 12.9 hours. Elvitegravir plasma exposures are non-linear and less than dose proportional, likely due to solubility-limited absorption.

**Cobicistat:** Cobicistat is 97-98% bound to human plasma proteins and the mean plasma to blood drug concentration ratio was 2.

Cobicistat is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [14C]cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and feces and do not contribute to the CYP3A inhibitory activity of cobicistat. Eighty-six percent and 8.2% of the dose were recovered in feces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of STRIBILD is approximately 3.5 hours and the associated cobicistat exposures provide elvitegravir  $C_{\text{trough}}$  approximately 10-fold above the protein-binding adjusted IC<sub>95</sub> for wild-type HIV-1 virus. Cobicistat exposures are non-linear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

### Effect of food

**Tenofovir disoproxil fumarate, emtricitabine, elvitegravir / cobicistat:** Relative to fasting conditions, the administration of STRIBILD with a light meal (~373 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) resulted in increased exposures of elvitegravir and tenofovir. For elvitegravir,  $C_{\text{max}}$  and AUC increased 22% and 36% with a light meal, while increasing 56% and 91% with a high-fat meal, respectively. The  $C_{\text{max}}$  and AUC of tenofovir increased 20% and 25% respectively with a light meal, while the  $C_{\text{max}}$  was unaffected and AUC increased 25% with a high fat meal. Cobicistat exposures were unaffected by a light meal and although there was a modest decrease of 24% and 18% in  $C_{\text{max}}$  and AUC respectively with a high-fat meal, no difference was observed in its pharmacoenhancing effect on elvitegravir. Emtricitabine exposures were unaffected with light or high-fat meal.

### Age, Gender and Ethnicity

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for cobicistat-boosted elvitegravir, emtricitabine, or tenofovir DF (see PRECAUTIONS).

The pharmacokinetics of elvitegravir or cobicistat in paediatric patients have not been established. Pharmacokinetics of elvitegravir, cobicistat, emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat-boosted elvitegravir, emtricitabine and tenofovir DF.

### Patients with Impaired Renal Function

**Tenofovir disoproxil fumarate and emtricitabine:** The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min or with end stage renal disease (ESRD) requiring dialysis,  $C_{\text{max}}$ , and  $AUC_{0-\infty}$  of emtricitabine and tenofovir were increased (see PRECAUTIONS).

**Elvitegravir and cobicistat:** A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No clinically relevant differences in elvitegravir or cobicistat



pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects.

### **Patients with Hepatic Impairment**

The pharmacokinetics of STRIBILD have not been studied in patients with hepatic impairment.

**Tenofovir disoproxil fumarate and emtricitabine:** The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine have not been studied in patient's hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

**Elvitegravir and cobicistat:** Both elvitegravir and cobicistat are primarily metabolized and eliminated by the liver. A study of pharmacokinetics of cobicistat-boosted elvitegravir was performed in non-HIV-1 infected subjects with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. No dosage adjustment of elvitegravir or cobicistat is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of elvitegravir or cobicistat has not been studied.

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

Pharmacokinetics of tenofovir DF and emtricitabine have not been fully evaluated in hepatitis B and/or C co-infected patients. Limited data from population pharmacokinetic analysis (N=24) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted elvitegravir.

### **Assessment of Drug Interactions**

The drug interaction studies described were conducted with STRIBILD, elvitegravir (coadministered with cobicistat or ritonavir), emtricitabine, or tenofovir DF.

As STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral medications, information regarding drug-drug interactions with other antiretrovirals agents is not provided (see PRECAUTIONS).

**Elvitegravir:** Elvitegravir is primarily metabolized by cytochrome CYP3A, and drugs that induce or inhibit CYP3A may affect the exposure of elvitegravir. Coadministration of STRIBILD with drugs that induce CYP3A may result in decreased plasma concentrations of elvitegravir and reduce the therapeutic effect of STRIBILD (see CONTRAINDICATIONS).

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 2. The effects of elvitegravir on the exposure of coadministered drugs are shown in Table 3.

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

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose	N	% Change of Elvitegravir Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
					C <sub>max</sub>	AUC	C <sub>min</sub>
Antacids	20 mL single dose ± 2 hours or ± 4 hours from elvitegravir administration	50 single dose	Ritonavir 100 single dose	39	Û	Û	Û
	20 mL single dose simultaneously administered with elvitegravir	50 single dose	Ritonavir 100 single dose	13	<sup>-</sup> 47 ( <sup>-</sup> 53 to <sup>-</sup> 40)	<sup>-</sup> 45 ( <sup>-</sup> 50 to <sup>-</sup> 40)	<sup>-</sup> 41 ( <sup>-</sup> 48 to <sup>-</sup> 33)
Ketoconazole	200 twice daily	150 once daily	Ritonavir 100 once daily	18	Û	- 48 (- 36 to - 62)	- 67 (- 48 to - 88)
Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	Û	<sup>-</sup> 21 ( <sup>-</sup> 26 to <sup>-</sup> 15)	<sup>-</sup> 67 ( <sup>-</sup> 73 to <sup>-</sup> 60)
Rosuvastatin	10 single dose	150 once daily	Cobicistat 150 once daily	10	Û	Û	Û

a. All interaction studies conducted in healthy volunteers

b. - = Increase; <sup>-</sup> = Decrease; Û = No Effect; NA = Not Applicable

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

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
					C <sub>max</sub>	AUC	C <sub>min</sub>
Buprenorphine	16-24 once daily	150 once daily	150 once daily	17	- 12 (- 2 to - 27)	- 35 (- 18 to - 55)	- 66 (- 43 to - 93)
Norbuprenorphine					- 24 (- 3 to - 49)	- 42 (- 22 to - 67)	- 57 (- 31 to - 88)
Naloxone	4-6 once daily	150 once daily	150 once daily	17	- 28 (- 39 to - 15)	- 28 (- 41 to - 13)	N/A
R-Methadone	80-120 daily	150 once daily	150 once daily	11	Û	Û	Û
S-Methadone					Û	Û	Û
Norgestimate/ ethinyl estradiol	0.180/0.215/ 0.250 norgestimate once daily	150 once daily <sup>c</sup>	Cobicistat 150 once daily <sup>c</sup>	13	- 108 (- 100 to - 117)	- 126 (- 115 to - 137)	- 167 (- 143 to - 192)
	0.025 ethinyl estradiol once daily				Û	- 25 (- 31 to - 19)	- 44 (- 48 to - 39)
Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	Û	Û	Û
25-O- desacetyl- rifabutin				12	- 384 (- 309 to - 474)	- 525 (- 408 to - 669)	- 394 (- 304 to - 504)
Rosuvastatin	10 single dose	150 single dose	Cobicistat 150 single dose	10	- 89 (- 48 to - 142)	- 38 (- 13 to	N/A

a. All interaction studies conducted in healthy volunteers

b. - = Increase; - = Decrease; Û = No Effect; NA = Not Applicable

c. Study conducted with STRIBILD

In drug interaction studies conducted with elvitegravir, neither famotidine, methadone (R/S-methadone) nor omeprazole had clinically significant effect on the C<sub>max</sub>, AUC, or C<sub>min</sub> of elvitegravir.

**Cobicistat:** Cobicistat is an inhibitor of cytochrome P450 (CYP3A), and is also a CYP3A substrate. Agents that are highly dependent on CYP3A metabolism and have high first pass metabolism are the most susceptible to large increases in exposure when coadministered with cobicistat. Agents that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentration of cobicistat (see CONTRAINDICATIONS).

**Tenofovir disoproxil fumarate and emtricitabine:** *In vitro* and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

Emtricitabine and tenofovir are 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 emtricitabine and tenofovir DF with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

In drug interaction studies conducted with emtricitabine and with tenofovir DF, coadministration of emtricitabine and famciclovir had no effect on the  $C_{max}$  or AUC of either drug, coadministration of tenofovir and entecavir had no effect on the  $C_{max}$  or AUC of either drug, and coadministration of tenofovir and ribavirin had no effect on the  $C_{max}$  and AUC of entecavir or ribavirin.

## CLINICAL TRIALS

The efficacy of STRIBILD is based on the analyses of 48-week data from two randomised, double-blind, active-controlled trials Study 102 and Study 103 in treatment-naïve, HIV-1 infected patients (N=1408) with baseline estimated creatinine clearance above 70 mL/min.

In Study 102, subjects were randomised in a 1:1 ratio to receive either STRIBILD (tenofovir DF 300 mg /emtricitabine 200 mg/elvitegravir 150 mg/cobicistat 150 mg N=348) once daily or ATRIPLA<sup>®</sup> (tenofovir DF 300 mg/emtricitabine 200 mg/ efavirenz 600 mg N=352) once daily. The mean age was 38 years (range 18-67), 89% were male, 63% were White, and 28% were Black. The mean baseline plasma HIV-1 RNA was 4.8 log<sub>10</sub> copies/mL (range 2.6–6.5). The mean baseline CD4+ cell count was 386 cells/mm<sup>3</sup> (range 3–1348) and 13% had CD4+ cell counts <200 cells/mm<sup>3</sup>. Thirty-three percent of subjects had baseline viral loads >100,000 copies/mL.

In Study 103, patients were randomised in a 1:1 ratio to receive either STRIBILD (tenofovir DF 300 mg /emtricitabine 200 mg/elvitegravir 150 mg/cobicistat 150 mg, N=353) once daily or ATV/r (atazanavir 300 mg + ritonavir 100 mg) + TRUVADA (tenofovir DF 300 mg/emtricitabine 200 mg) (N=355) once daily. The mean age was 38 years (range 19-72), 90% were male, 74% were White, 17% were Black, and 5% were Asian. The mean baseline plasma HIV-1 RNA was 4.8 log<sub>10</sub> copies/mL (range 1.7-6.6). The mean baseline CD4+ cell count was 370 cells/mm<sup>3</sup> (range 5-1132) and 13% had CD4+ cell count <200 cells/mm<sup>3</sup>. Forty percent of subjects had baseline viral loads >100,000 copies/mL.

In both studies, patients were stratified by baseline HIV-1 RNA ( $\leq$  100,000 copies/mL or >100,000 copies/mL).

Treatment outcomes of Study 102 and Study 103 through 48 weeks are presented in Table 4.

**Attachment 1: Product information for AusPAR Stribild; tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat; Gilead Sciences Pty Ltd; PM-2011-03533-3-2. Date of Finalisation 5 August 2013. This Product Information was approved at the time this AusPAR was published.**

**Table 4 Virologic Outcome of Randomised Treatment of Study 102 and Study 103 at Week 48<sup>a</sup>**

	Study 102		Study 103	
	STRIBILD (N=348)	ATRIPLA (N=352)	STRIBILD (N=353)	ATV/r + TRUVADA (N=355)
<b>Virologic Success</b> HIV-1 RNA < 50 copies/mL	88%	84%	90%	87%
Treatment Difference	3.6% (95% CI = -1.6%, 8.8%)		3.0% (95% CI = -1.9%, 7.8%)	
<b>Virologic Failure</b>	7%	7%	5%	5%
<b>No Virologic Data at Week 48 Window</b>				
Discontinued Study Drug Due to AE or Death <sup>b</sup>	3%	5%	3%	5%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL <sup>c</sup>	2%	3%	2%	3%
Missing Data During Window but on Study Drug	0%	0%	0%	0%

a. Week 48 window is between Day 309 and 378 (inclusive).

b. Includes patients who discontinued due to adverse event 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.

c. Includes patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

STRIBILD met the noninferiority criteria in achieving HIV-1 RNA < 50 copies/mL when compared to ATRIPLA and when compared to ATV/r + TRUVADA.

In Study 102, the mean increase from baseline in CD4+ cell count at Week 48 was 239 cells/mm<sup>3</sup> in the STRIBILD treated patients and 206 cells/mm<sup>3</sup> in the ATRIPLA-treated patients. In Study 103, the mean increase from baseline in CD4+ cell count at Week 48 was 207 cells/mm<sup>3</sup> in the STRIBILD-treated patients and 211 cells/mm<sup>3</sup> in the ATV/r + TRUVADA-treated patients.

## INDICATIONS

STRIBILD is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naive adults.

STRIBILD is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

## CONTRAINDICATIONS

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

STRIBILD must not be administered to children or adolescents under the age of 18 years.



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Coadministration with the following drugs is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to STRIBILD (See Drug Interactions):

- Alpha 1-adrenoreceptor antagonists: alfuzosin
- Antimycobacterials: rifampicin
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- GI motility agents: cisapride
- Herbal products: St. John's wort (*Hypericum perforatum*)
- HMG CoA reductase inhibitors: lovastatin, simvastatin
- Neuroleptics: pimozide
- PDE-5 inhibitors: sildenafil for the treatment of pulmonary arterial hypertension
- Sedative/hypnotics: orally administered midazolam, triazolam

STRIBILD is a fixed-dose combination of tenofovir DF, emtricitabine, elvitegravir and cobicistat. STRIBILD should not be administered concurrently with other medicinal products containing any of the same active components: VIREAD (tenofovir DF), EMTRIVA (emtricitabine), TRUVADA (tenofovir DF / emtricitabine combination tablet), ATRIPLA (tenofovir DF / emtricitabine / efavirenz combination tablet), EVIPLERA™ (tenofovir DF / emtricitabine / rilpivirine). STRIBILD should not be administered with HEPSERA® (adefovir dipivoxil).

## **PRECAUTIONS**

### **General**

Patients receiving STRIBILD 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.

Patients should be advised that antiretroviral therapies, including STRIBILD, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that STRIBILD 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 including the tenofovir DF component of STRIBILD, alone or 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 STRIBILD 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).

## **Renal Impairment**

The emtricitabine and tenofovir DF components of STRIBILD are primarily excreted by the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and Fanconi syndrome have been reported with the use of tenofovir DF.

Estimated creatinine clearance, urine glucose, and urine protein should be documented in all patients prior to initiating therapy with STRIBILD. STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL/min.

Routine monitoring of estimated creatine clearance should be performed during STRIBILD therapy in patients, additionally, serum phosphorous should be measured in patients at risk for renal impairment. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL/min as dose interval adjustment required for tenofovir disoproxil fumarate and emtricitabine cannot be achieved with the fixed-dose combination tablet.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be monitored for renal safety, including measuring serum phosphorous, urine glucose and urine protein (see ADVERSE EFFECTS, CLINICAL TRIALS).

STRIBILD should be avoided with concurrent or recent use of a nephrotoxic agent.

## **Hepatic Impairment**

STRIBILD has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, STRIBILD is not recommended for use in patients with severe hepatic impairment.

## **Bone Effects**

Bone toxicity including a reduction in bone mineral density (BMD) have been observed in tenofovir DF studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) with VIREAD. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see ADVERSE EVENTS). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained. If bone abnormalities are suspected, then appropriate consultation should be obtained.

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

The safety and efficacy of STRIBILD have not been established in patients coinfecting with HBV and HIV-1. Discontinuation of STRIBILD therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine and tenofovir DF components of STRIBILD. 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 STRIBILD treatment. If appropriate, resumption 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**

STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be coadministered with other antiretroviral products. STRIBILD should not be used in conjunction with protease inhibitors or non-nucleoside reverse transcriptase inhibitors due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of cobicistat, elvitegravir, and/or the coadministered antiretroviral products.

STRIBILD should not be coadministered with products containing any of the same active components, emtricitabine or tenofovir disoproxil fumarate; or with products containing lamivudine. STRIBILD should not be administered concurrently with ritonavir or ritonavir-containing products or regimens due to similar effects of cobicistat and ritonavir on CYP3A. STRIBILD should not be administered with adefovir dipivoxil.

## **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 tenofovir DF and emtricitabine. 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 are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

## **Impairment of Fertility**

No reproductive toxicity studies have been conducted with tenofovir DF, emtricitabine, and elvitegravir and cobicistat in combination.

**Tenofovir disoproxil fumarate:** Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir DF dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

**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).

**Elvitegravir:** Elvitegravir did not affect fertility in male and female rats at a dose achieving greater than 10 fold higher exposures (AUC), than in humans with the therapeutic 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 18-fold higher than human exposures at the recommended 150 mg daily dose.

**Cobicistat:** Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) greater than 4-fold higher than human exposures with the 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 1.2-fold higher than human exposures at the recommended 150 mg daily dose.

### **Use in Pregnancy**

Pregnancy Category B3.

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

**Tenofovir disoproxil fumarate:** Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the fetus due to tenofovir at respective exposures (AUC) of 4-13 and 66-fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced fetal serum phosphorus concentrations.

**Emtricitabine:** No evidence of embryofetal 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.

**Elvitegravir:** Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended dose of 150 mg/day.

**Cobicistat** Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 1.8 and 4.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

### **Use in Lactation**

It is not known whether elvitegravir and cobicistat are excreted in human milk.

Studies in rats have demonstrated that elvitegravir and cobicistat are secreted into milk.

**Tenofovir disoproxil fumarate:** In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low concentrations (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC<sub>50</sub> (50% maximal inhibitory concentration)). Tenofovir associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

**Emtricitabine:** Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC<sub>50</sub> but 3 to 12 times lower than the C<sub>min</sub> (minimal expected trough concentrations in adults) achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine 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 STRIBILD.

### **Animal Toxicology**

**Tenofovir disoproxil fumarate:** Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying



degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

### **Use in Children**

STRIBILD is not recommended for use in children or adolescents below 18 years of age due to insufficient data on safety and efficacy.

### **Use in the Elderly**

Clinical studies of STRIBILD did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing STRIBILD to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

### **Genotoxicity**

No genotoxicity studies have been conducted with tenofovir DF, emtricitabine, elvitegravir and cobicistat in combination.

*Tenofovir disoproxil fumarate* was mutagenic in an *in vitro* mouse L5178Y lymphoma cell assay (tk locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage.

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

*Elvitegravir* showed an equivocal response in an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, but only in the absence of metabolic activation. No genotoxicity was observed in a test for bacterial reverse mutation *in vitro*, or *in vivo* rat micronucleus test.

*Cobicistat* was not genotoxic in *in vitro* tests for bacterial reverse gene mutation or gene mutation in mouse lymphoma L5178Y cells (tk locus), or in an *in vivo* rat micronucleus test.

### **Carcinogenicity**

No carcinogenicity studies have been conducted with tenofovir DF, emtricitabine, elvitegravir and cobicistat in combination.

*Tenofovir disoproxil fumarate*: In a long-term carcinogenicity study conducted in mice with tenofovir DF there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

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**Emtricitabine:** In long-term oral carcinogenicity studies conducted with emtricitabine, 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).

**Elvitegravir:** In a long-term carcinogenicity study in mice, no tumourigenic response was seen with doses of up to 2000 mg/kg/day, with the highest dose also being given together with 25 mg/kg/day ritonavir. Respective elvitegravir exposures (AUC) with this dose were approximately 3.1 and 14 times the human exposure with the 150 mg/day dose. No tumourigenic response was seen in a long-term study in rats with doses up to 2000 mg/kg/day (12 times in males and 27 times in females the human exposure (AUC) with the therapeutic dose).

**Cobicistat:** In a long term study in mice with doses of up to 50 mg/kg/day in males and 100 mg/kg/day in females (9-21 times the human exposure (AUC) at 150mg daily), cobicistat treatment did not result in any increased tumour incidences. In a corresponding study, with doses of up to 50 mg/kg/day in males and 30 mg/kg/day in females (1.9-2.6 times the human exposure with 150 mg daily), treatment resulted in increased incidence of thyroid follicular cell tumours. Hepatocyte hypertrophy was also observed, and this oncogenic response is most likely related to alterations in thyroid hormones and to be specific to species.

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

### **General**

As STRIBILD contains tenofovir DF, emtricitabine, elvitegravir and cobicistat, any interactions that have been identified with these agents individually may occur with STRIBILD.

### **CYP3A Associated Drug-Drug Interactions**

Cobicistat, a component of STRIBILD, is a strong inhibitor of cytochrome P450 (CYP3A) and a CYP3A substrate. Thus, coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs. Coadministration of STRIBILD with drugs that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentration of cobicistat. Cobicistat, is also an inhibitor of CYP2D6. The transporters that cobicistat inhibits included p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Thus, coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

Elvitegravir, a component of STRIBILD, is metabolized by CYP3A. Drugs that induce CYP3A activity are expected to increase the clearance of elvitegravir and cobicistat, resulting in decreased plasma concentration of elvitegravir and cobicistat, which may lead to loss of therapeutic effect of STRIBILD and development of resistance.

### **Drugs Affecting Renal Functions**

Tenofovir and emtricitabine and are 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 STRIBILD with drugs that are eliminated by active tubular secretion may increase concentrations of Tenofovir and emtricitabine, and/or the coadministered drug. Some examples include, but are not limited to

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acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of tenofovir and / or emtricitabine.

### **Co-administration of other medicinal products**

Exposure to didanosine is significantly increased following co-administration with tenofovir DF that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see Established and Other Potentially Significant Interactions).

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

STRIBILD is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral products. Therefore, information regarding drug-drug interactions with other antiretroviral products (including protease inhibitors and non-nucleoside reverse transcriptase inhibitors) is not provided. Drug interaction information for STRIBILD with potential concomitant drugs is summarized in Table 5. The drug interactions described are based on studies conducted with the components of STRIBILD, (tenofovir DF, emtricitabine, elvitegravir and cobicistat) as individual agents and/or in combination, or are potential drug interactions that may occur with STRIBILD. No drug interaction studies have been conducted using STRIBILD except for a study of oral contraceptives.

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

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**Table 5      Established Significant <sup>a</sup> Drug Interactions**

<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>Acid Reducing Agents:</b> antacids	- elvitegravir	Elvitegravir plasma concentrations are lower with antacids due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate STRIBILD and antacid administration by at least 2 hours.  For information on other acid reducing agents (e.g. H <sub>2</sub> -receptor antagonists and proton pump inhibitors), see <i>Drugs Without Clinically Significant Interactions</i> .
<b>Alpha 1-Adrenoreceptor Antagonist:</b> alfuzosin	- alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions.  Coadministration of STRIBILD and alfuzosin is contraindicated.
<b>Analeptics:</b> modafinil	- elvitegravir - cobicistat	Coadministration of modafinil, a CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.  Alternative analeptics should be considered when administering with STRIBILD.
<b>Antiarrhythmics:</b> amiodarone disopyramide flecainide systemic lidocaine propafenone digoxin	- antiarrhythmics - digoxin	Concentrations of these antiarrhythmic drugs may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with STRIBILD.
<b>Antibacterials:</b> clarithromycin telithromycin	- clarithromycin - telithromycin - cobicistat	Concentrations of clarithromycin and/or cobicistat may be altered with coadministration of STRIBILD.  No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (CLcr 60-90 mL/min). Clinical monitoring is recommended for patients with CLcr <90 mL/min. For patients with CLcr <60 mL/min, alternative antibacterials should be considered when administering STRIBILD.  Concentrations of telithromycin and/or cobicistat may be altered with co-administration of STRIBILD. Clinical monitoring is recommended upon co-administration with STRIBILD.
<b>Anticoagulants:</b> warfarin	- or - warfarin	Concentrations of warfarin may be affected upon coadministration with STRIBILD. It is recommended that the international normalized ratio (INR) be monitored upon coadministration of STRIBILD.

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<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>Anticonvulsants:</b> carbamazepine oxcarbazepine phenytoin  clonazepam ethosuximide	- elvitegravir  - cobicistat  - clonazepam  - ethosuximide	Coadministration of phenobarbital, phenytoin, carbamazepine, and oxcarbazepine, CYP3A inducers, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered when administering with STRIBILD.  Concentrations of clonazepam and ethosuximide may be increased when coadministered with cobicistat. Clinical monitoring is recommended upon coadministration of STRIBILD.
<b>Antidepressants:</b> Selective Serotonin Reuptake Inhibitors (SSRIs)  trazodone	- SSRIs  - trazodone	Concentrations of these antidepressant agents may be increased when coadministered with cobicistat. Dose titration may be required for most drugs of the SSRI class.  Concentrations of trazodone may increase upon coadministration with cobicistat. Dose reduction should be considered when administering trazodone with STRIBILD.
<b>Antifungals:</b> itraconazole ketoconazole voriconazole	- antifungals  - cobicistat	Concentrations of ketoconazole and/or cobicistat may increase with coadministration of STRIBILD. When administering with STRIBILD, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg per day.  Concentrations of voriconazole may be increased when coadministered with cobicistat. Clinical monitoring may be needed upon coadministration with STRIBILD.
<b>Anti-gout:</b>  colchicine	- colchicine	Dose reductions of colchicine may be required. STRIBILD should not be coadministered with colchicine in patients with renal or hepatic impairment.
<b>Antihistamines:</b> astemizole terfenadine	- astemizole  - terfenadine	Concentrations of astemizole and terfenadine may be increased when coadministered with cobicistat. Clinical monitoring is recommended when these agents are coadministered with STRIBILD.
<b>Antimycobacterial:</b> rifabutin rifapentine	- elvitegravir  - cobicistat	Coadministration of, rifabutin, and rifapentine with STRIBILD may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.  Coadministration of STRIBILD with rifabutin or rifapentine is not recommended.
<b>Beta-Blockers:</b> metoprolol timolol	- beta-blockers	Concentrations of beta-blockers may be increased when coadministered with cobicistat. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with STRIBILD.



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<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>Calcium Channel Blockers:</b> amlodipine diltiazem felodipine nifedipine verapamil	- calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration with STRIBILD.
<b>Corticosteroid: Systemic:</b> dexamethasone	- elvitegravir - cobicistat	Coadministration of dexamethasone, a CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.  Alternative systemic corticosteroids should be considered.
<b>Corticosteroids: Inhaled/Nasal:</b> fluticasone	- fluticasone	Concomitant use of inhaled or nasal fluticasone and STRIBILD may increase plasma concentrations of fluticasone, resulting in reduced serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use.
<b>Endothelin Receptor Antagonists:</b> bosentan	- bosentan - elvitegravir - cobicistat	Coadministration with STRIBILD may lead to decreased elvitegravir and/or cobicistat exposures and loss of therapeutic effect. Coadministration is not recommended.
<b>Ergot Derivatives:</b> dihydroergotamine ergotamine ergonovine methylergonovine	- ergot derivatives	Ergot derivatives are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions.  Coadministration of STRIBILD and dihydroergotamine, ergotamine, ergonovine and methylergonovine are contraindicated.
<b>Herbal Products:</b> St. John's wort (Hypericum perforatum)	- elvitegravir - cobicistat	Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.  Coadministration of STRIBILD and St. John's wort is contraindicated.

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<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>HMG CoA Reductase Inhibitors:</b> atorvastatin lovastatin rosuvastatin simvastatin	- HMG-CoA reductase inhibitors	HMG CoA reductase inhibitors are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of lovastatin or simvastatin, which are associated with the potential for serious and/or life-threatening reactions.  Coadministration of STRIBILD and lovastatin and simvastatin are contraindicated.  Concentrations of atorvastatin may be increased when administered with elvitegravir and cobicistat. Start with the lowest possible dose of atorvastatin with careful monitoring upon coadministration with STRIBILD.  Concentrations of rosuvastatin are transiently increased when administered with elvitegravir and cobicistat. Dose modifications are not necessary when rosuvastatin is administered in combination with STRIBILD.
<b>Immunosuppressants:</b> cyclosporine sirolimus tacrolimus	- immunosuppressants	Concentrations of these immunosuppressant agents may be increased when administered with cobicistat. Therapeutic monitoring is recommended upon coadministration with STRIBILD.
<b>Narcotic Analgesics:</b> Methadone  Buprenorphine/naloxone	Û R- Methadone Û S- Methadone  - buprenorphine - norbuprenorphine - naloxone	Methadone exposures are unaffected upon coadministration with elvitegravir and cobicistat. No dose adjustment of methadone is required upon coadministration with STRIBILD.  Concentrations of buprenorphine and norbuprenorphine are modestly increased and concentrations of naloxone are modestly decreased when coadministered with elvitegravir and cobicistat, with no changes on opioid pharmacodynamics. Accordingly, the observed concentration changes are not considered clinically relevant and no dose adjustment of buprenorphine/naloxone is required upon coadministration with STRIBILD.
<b>Inhaled Beta Agonist:</b> salmeterol	- salmeterol	Coadministration with STRIBILD may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life-threatening reactions. Concurrent administration of salmeterol and STRIBILD is not recommended.
<b>Neuroleptics:</b> perphenazine risperidone	- neuroleptics	For-neuroleptics, consider reducing the dose of the neuroleptic upon coadministration with STRIBILD.

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<b>Concomitant Drug Class: Drug Name</b>	<b>Effect<sup>b</sup></b>	<b>Clinical Comment</b>
<b>Phosphodiesterase-5 (PDE5) Inhibitors:</b> sildenafil tadalafil vardenafil	- PDE5 inhibitors	PDE5 inhibitors are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE5 inhibitor-associated adverse reactions.  Coadministration of STRIBILD and sildenafil for the treatment of pulmonary arterial hypertension are contraindicated while co administration of STRIBILD with tadalafil is not recommended.  For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours or tadalafil no more than 10 mg in 72 hours be coadministered with STRIBILD.  Vardenafil should not be coadministered with STRIBILD.
<b>Sedative/hypnotics:</b> buspirone clorazepate diazepam orally-administered midazolam triazolam zolpidem	- sedatives/hypnotics	Midazolam and triazolam are primarily metabolized by CYP3A. Coadministration with STRIBILD may result in increased plasma concentrations of these drugs, which are associated with the potential for serious and/or life-threatening reactions.  Coadministration of STRIBILD and orally administered midazolam and triazolam are contraindicated. With other sedative/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.
<b>Hormonal Contraceptives:</b> norgestimate/ ethinyl oestradiol	- norgestimate - ethinyl oestradiol	The effects of increases in the concentration of the progestational component of norgestimate are not fully known and can include increased risk of insulin resistance, dyslipidemia, acne and venous thrombosis. The potential risks and benefits associated with coadministration of norgestimate/ethinyl oestradiol with STRIBILD should be considered, particularly in women who have risk factors for these events.  Coadministration of STRIBILD with other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptive containing progestones other than norgestimate has not been studied; therefore alternative (non hormonal) method of contraception can be considered.

a. This table is not all inclusive.

b. - = increase, ∩ = decrease, ↔ = no effect

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

Based on drug interaction studies conducted with the components of STRIBILD, no clinically significant drug interactions have been either observed or are expected between the components of STRIBILD and the following drugs: entecavir, famciclovir, famotidine, R/S-methadone, omeprazole, and ribavirin.

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

No studies on the effects of STRIBILD on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with STRIBILD.

### **ADVERSE EFFECTS**

As STRIBILD contains tenofovir DF, emtricitabine, elvitegravir and cobicistat, adverse events associated with these individual antiretroviral agents may be expected to occur with the fixed combination tablet.

For additional safety information about VIREAD (tenofovir DF), EMTRIVA (emtricitabine) in combination with other antiretroviral agents, consult the Product Information for these products.

### **CLINICAL TRIALS**

The safety assessment of STRIBILD is based on pooled data from 1408 patients in the Phase 3 trials Study 102 and Study 103 in antiretroviral treatment-naïve HIV-1 infected adult patients. A total of 701 patients received STRIBILD once daily for 48 weeks.

The proportion of patients who discontinued treatment with STRIBILD, ATRIPLA or atazanavir/r + TRUVADA due to adverse events, regardless of severity, was 3.7%, 5.1% and 5.1%, respectively. The most common adverse reactions (incidence greater than or equal to 4%) occurring in patients receiving STRIBILD in studies 102 and 103 include diarrhea and headache. See also Table 6 for the frequency of adverse reaction (Grade 2-4) occurring in at least 2% of subjects in any treatment group in Studies 102 and 103.

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**Table 6 Treatment-Emergent Adverse Drug Reactions<sup>a</sup> (Grades 2-4) Reported in  $\geq$  2% of Subjects Receiving STRIBILD in Studies 102 and 103 (Week 48 analysis)**

	STRIBILD	ATRIPLA	Atazanavir/r + TRUVADA
	N=701	N=352	N=355
<b>GASTROINTESTINAL DISORDERS</b>			
Diarrhea	6%	4%	8%
Nausea	3%	3%	3%
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
Fatigue	2%	4%	4%
<b>INFECTIONS AND INFESTATIONS</b>			
Upper respiratory tract infection	4%	3%	3%
Bronchitis	4%	3%	3%
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
Back pain	2%	2%	2%
<b>NERVOUS SYSTEM DISORDERS</b>			
Headache	4%	1%	3%
<b>PSYCHIATRIC DISORDERS</b>			
Depression	3%	7%	3%

a. Frequencies of adverse reactions are based on grade 2- 4 treatment-emergent adverse events, regardless of relationship to study drugs

Treatment-emergent adverse drug reactions of at least moderate intensity ( $\geq$  Grade 2) that occurred in less than 2% of patients treated with STRIBILD in Studies 102 and 103 include vomiting, abdominal pain, dyspepsia, flatulence, dizziness, insomnia, abnormal dreams, renal failure, Fanconi syndrome acquired, blood creatinine increased, and rash.

Of the 701 patients who received STRIBILD for 48 weeks in Studies 102 and 103, renal events with laboratory findings consistent with proximal renal tubular injury leading to STRIBILD discontinuation were reported in 4 patients. These findings, largely reversed upon discontinuation of STRIBILD without clinical sequelae. All 4 patients had renal impairment at baseline or were at risk for renal impairment (see PRECAUTIONS).

**Tenofovir disoproxil fumarate and emtricitabine:** In addition to the adverse drug reactions observed with STRIBILD, the following adverse drug reactions occurred in at least 5% of treatment-experienced or treatment-naive patients receiving emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: fever, pain, nasopharyngitis, pneumonia, sinusitis, arthralgia, myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

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Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

**Laboratory Abnormalities:** The frequency of treatment-emergent laboratory abnormalities (Grade 3-4) occurring in at least 2% of subjects receiving STRIBILD in Studies 102 and 103 are presented in Table 7.

**Table 7: Laboratory Abnormalities (Grades 3-4) Reported in  $\geq$  2% of Subjects Receiving STRIBILD in Studies 102 and 103 (Week 48 analysis)**

	STRIBILD	ATRIPLA	Atazanavir/r + TRUVADA
<b>Laboratory Parameter Abnormality</b>	N=701	N=352	N=355
AST (>5.0 x ULN)	2%	3%	4%
Amylase* (>2.0 x ULN)	2%	2%	4%
Creatine Kinase ( <sup>3</sup> 10.0 x ULN)	5%	11%	7%
Urine RBC (Hematuria) (> 75 RBC/HPF)	3%	1%	2%

\* For subjects with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 3-4) occurring in STRIBILD (N=58), ATRIPLA (N=33), and Atazanavir/r + TRUVADA (N=33) was 12%, 15%, and 21%, respectively.

**Tenofovir disoproxil fumarate or emtricitabine:** In addition to the laboratory abnormalities observed with STRIBILD, the following laboratory abnormalities have been previously reported in patients treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: Grade 3 or 4 laboratory abnormalities of ALT (M: >215 U/L; F: >170 U/L), alkaline phosphatase (>550 U/L), bilirubin (>2.5 x ULN), serum glucose (<40 or >250 mg/dL), glycosuria ( $\geq$ 3+), neutrophils (<750/mm<sup>3</sup>), fasting cholesterol (>240 mg/dL), and fasting triglycerides (>750 mg/dL).

The cobicistat component of STRIBILD has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In Studies 102 and 103, decreases in estimated creatinine clearance occurred early in treatment with STRIBILD, after which they stabilized. The mean $\pm$ SD change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.9 14.9 mL/min for STRIBILD, -1.6  $\pm$ 16.5 mL/min for ATRIPLA, and -9.3 $\pm$ 15.8 mL/min for ATV/r+TRUVADA.

## POST MARKETING SURVEILLANCE

In addition to adverse events reported from clinical trials, the following events have been reported in post marketing surveillance. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

### Tenofovir disoproxil fumarate

#### IMMUNE SYSTEM DISORDERS

Allergic reaction (including angioedema), immune reconstitution syndrome



## **METABOLISM AND NUTRITION DISORDERS**

Lactic acidosis, hypokalaemia, hypophosphataemia

## **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS**

Dyspnoea

## **GASTROINTESTINAL DISORDERS**

Increased amylase, abdominal pain, pancreatitis

## **HEPATOBIILIARY DISORDERS**

Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

## **SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

Rash

## **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS**

Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures)

## **RENAL AND URINARY DISORDERS**

Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

## **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS**

Asthaenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir DF therapy in the absence of proximal renal tubulopathy.

### *Exacerbations of Hepatitis after Discontinuation of Treatment*

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see PRECAUTIONS).

### *Emtricitabine*

## **IMMUNE SYSTEM DISORDERS**

Immune reconstitution syndrome

## **DOSAGE AND ADMINISTRATION**

*Adults:* The recommended dose of STRIBILD is one tablet once daily taken orally with a meal.

*Renal impairment:* STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL/min. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL/min during treatment with STRIBILD as dose interval adjustment required

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for emtricitabine and tenofovir DF cannot be achieved with the fixed-dose combination tablet (see PRECAUTIONS).

## OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with STRIBILD 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).

**Tenofovir disoproxil fumarate:** Clinical experience of doses higher than the therapeutic dose of VIREAD 300 mg is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day of tenofovir DF, was administered daily for 7 days. In the second study, 600 mg of tenofovir DF was administered to patients orally for 28 days. No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

**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 emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

**Elvitegravir:** Limited clinical experience is available at doses higher than the therapeutic dose of elvitegravir. In one study, boosted elvitegravir equivalent to 2 times the therapeutic dose of 150 mg once daily for 10 days was administered to 42 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As elvitegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

**Cobicistat:** Limited clinical experience is available at doses higher than the therapeutic dose of cobicistat. In two studies, single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

## PRESENTATION AND STORAGE CONDITIONS

STRIBILD is available as tablets. Each tablet contains 300 mg tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil), 200 mg emtricitabine, 150 mg of elvitegravir and 150 mg of cobicistat. The tablets are film-coated, capsule shaped and green in colour. Each tablet is

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debossed with 'GSI' on one side and the number "1" surrounded by a square box (1) on the other side.

STRIBILD 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.

STRIBILD should be stored below 25 °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:**

22 February 2013

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