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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STRIBILD safely and effectively. See full prescribing information for STRIBILD.

STRIBILD™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Tablets, for oral use

Initial U.S. Approval: 2012

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of STRIBILD. (5.1)**
- **STRIBILD is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued EMTRIVA or VIREAD, two of the components of STRIBILD. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)**

----------INDICATIONS AND USAGE----------

STRIBILD, a combination of 1 integrase strand transfer inhibitor, 1 pharmacokinetic enhancer, and 2 nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors, is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose: One tablet taken once daily with food. (2)
- Dosing in renal impairment: STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL per minute. Discontinue in patients with estimated creatinine clearance below 50 mL per minute. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate. (3)

----------CONTRAINDICATIONS----------

- Coadministration of STRIBILD with drugs that:
  - are highly dependaent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events. (4)
  - strongly induce CYP3A which may lead to lower exposure of one or more components and loss of efficacy of STRIBILD which may result in loss of virologic response and possible resistance. (4)

----------WARNINGS AND PRECAUTIONS----------

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CLcr), urine glucose and urine protein before initiating treatment with STRIBILD. Monitor CLcr, urine glucose, and urine protein in all patients. Monitor serum phosphorus in patients at risk for renal impairment. Avoid administering STRIBILD with concurrent or recent use of nephrotoxic drugs. (5.3)
- Coadministration with other products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate including ATRIPLA, COMPLERA, EMTRIVA, TRUVADA, or VIREAD; with drugs containing lamivudine; or with drugs or regimens containing ritonavir. Do not administer in combination with HEPSERA. (5.4)
- Decreases in bone mineral density (BMD): Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.5)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.6)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse drug reactions to STRIBILD (incidence greater than or equal to 10%, all grades) are nausea and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- STRIBILD is a complete regimen for the treatment of HIV-1 infection; therefore, STRIBILD should not be administered with other antiretroviral medications for treatment of HIV-1 infection. (5.4, 7)
- STRIBILD can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of one or more components of STRIBILD. Consult the full prescribing information prior to and during treatment for potential drug-drug interactions. (4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Nursing mothers: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of STRIBILD, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*.

STRIBILD is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of STRIBILD have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and human immunodeficiency virus-1 (HIV-1) and have discontinued EMTRIVA or VIREAD, which are components of STRIBILD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue STRIBILD. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

1 INDICATION AND USAGE

STRIBILD™ is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve.

2 DOSAGE AND ADMINISTRATION

The recommended dose of STRIBILD is one tablet taken orally once daily with food *[See Clinical Pharmacology (12.3)]*.

Renal Impairment: STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL per min. Because STRIBILD is a fixed-dose combination tablet, STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL per min during treatment with STRIBILD as dose interval adjustment required for emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) cannot be achieved *[See Warnings and Precautions (5.3), Adverse Reactions (6.1), Use in Specific Populations (8.6), Clinical Pharmacology (12.3), and Clinical Studies (14)].*

Hepatic Impairment: No dose adjustment of STRIBILD is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of STRIBILD in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, STRIBILD is not recommended for use in patients with severe hepatic impairment *[See Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].*

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3 DOSAGE FORMS AND STRENGTHS

STRIBILD is available as tablets. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate (tenofovir DF, equivalent to 245 mg of tenofovir disoproxil).

The tablets are green, capsule-shaped, film-coated, debossed with "GSI" on one side and the number "1" surrounded by a square box (1) on the other side of the tablet.

4 CONTRAINDICATIONS

Coadministration of STRIBILD is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs and other contraindicated drugs (which may lead to reduced efficacy of STRIBILD and possible resistance) are listed in Table 1 *[See Drug Interactions (7.4), Clinical Pharmacology (12.3)].*

Table 1 Drugs that are Contraindicated with STRIBILD

Drug Class	Drugs within class that are contraindicated with STRIBILD	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antimycobacterial	Rifampin	Rifampin is a potent inducer of CYP450 metabolism. STRIBILD should not be used in combination with rifampin, as this may cause significant decrease in the plasma concentration of elvitegravir and cobicistat. This may result in loss of therapeutic effect to STRIBILD.
Ergot Derivatives	Dihydroergotamine Ergotamine Methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening events such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking STRIBILD should not use products containing St. John's wort because coadministration may result in reduced plasma concentrations of elvitegravir and cobicistat. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin Simvastatin	Potential for serious reactions such as myopathy, including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening events such as cardiac arrhythmias.
Phosphodiesterase-5	Sildenafil[a] when dosed as REVATIO	A safe and effective dose in combination with STRIBILD has not been established for sildenafil

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(PDE5) Inhibitor	for the treatment of pulmonary arterial hypertension	(REVATIO) when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Sedative/hypnotics	Triazolam Orally administered midazolam[b]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with STRIBILD may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

a. See Drug Interactions (7), Table 5 for sildenafil when dosed as VIAGRA for erectile dysfunction.

b. See Drug Interactions (7), Table 5 for parenterally administered midazolam.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir DF, a component of STRIBILD, in combination with other antiretrovirals. 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 analogs 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).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. STRIBILD is not approved for the treatment of chronic HBV infection and the safety and efficacy of STRIBILD have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of STRIBILD. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with STRIBILD. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

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5.3 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF and with the use of STRIBILD *[See Adverse Reactions (6.2)]*.

In the clinical trials of STRIBILD over 48 weeks (N=701), 8 (1.1%) subjects in the STRIBILD group and 1 (0.1%) subject in the combined comparator groups discontinued study drug due to a renal adverse event. Four (0.6%) of the subjects who received STRIBILD developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of STRIBILD compared to none in the comparator groups. Two of these four subjects had renal impairment (i.e. estimated creatinine clearance less than 70 mL per min) at baseline. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved but did not completely resolve in all subjects upon discontinuation of STRIBILD. Renal replacement therapy was not required for these subjects.

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

Routine monitoring of estimated creatinine clearance, urine glucose, and urine protein should be performed during STRIBILD therapy in all patients. Additionally, serum phosphorus should be measured in patients at risk for renal impairment.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function *[See Adverse Reactions (6.1)]*, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.

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

The emtricitabine and tenofovir DF components of STRIBILD are primarily excreted by the kidney. STRIBILD should be discontinued if estimated creatinine clearance declines below 50 mL per min as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved with the fixed-dose combination tablet.

5.4 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.

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STRIBILD should not be coadministered with products containing any of the same active components, emtricitabine or tenofovir DF (ATRIPLA, COMPLERA, EMTRIVA, TRUVADA, VIREAD); or with products containing lamivudine (COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR). STRIBILD should not be administered with adefovir dipivoxil (HEPSERA).

5.5 Decreases in Bone Mineral Density

In previous clinical trials, tenofovir DF has been associated with decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1.25 Vitamin D levels were also higher in subjects receiving VIREAD. The effects of tenofovir DF-associated changes in BMD on future fracture risk are unknown. For additional information, please consult the VIREAD prescribing information.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF *[See Adverse Reactions (6.2)]*.

In Study 103, BMD was assessed by DEXA in a non-random subset of 120 subjects. Mean percentage decreases in BMD from baseline to Week 48 in the STRIBILD group (N = 54) were comparable to the atazanavir + ritonavir + TRUVADA group (N = 66) at the lumbar spine (-2.6% versus -3.3%, respectively) and at the hip (-3.1% versus -3.9%, respectively). In Studies 102 and 103, bone fractures occurred in 9 subjects (1.3%) in the STRIBILD group, 6 subjects (1.7%) in the ATRIPLA group, and 6 subjects (1.7%) in the atazanavir + ritonavir + TRUVADA group. These findings were consistent with data from an earlier 144-week trial of treatment-naïve subjects receiving tenofovir DF + lamivudine + efavirenz.

Assessment of BMD should be considered for HIV-1 infected patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial in all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

5.6 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including STRIBILD. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.3)]*.
- Decreases in Bone Mineral Density *[See Warnings and Precautions (5.5)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.7)]*.

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of STRIBILD is based on pooled data from 1408 subjects in two comparative clinical trials, Study 102 and Study 103, in antiretroviral treatment-naive HIV-1 infected adult subjects. A total of 701 subjects received STRIBILD once daily for at least 48 weeks.

The proportion of subjects who discontinued treatment with STRIBILD, ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg) or atazanavir + ritonavir + TRUVADA (emtricitabine 200 mg/tenofovir DF 300 mg) due to adverse events, regardless of severity, was 3.7%, 5.1% and 5.1%, respectively. Table 2 displays the frequency of adverse drug reactions greater than or equal to 5%.

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Table 2 Treatment-Emergent Adverse Drug Reactions[a] (all grades) Reported in ≥ 5% of Subjects in Any Treatment Arm in Studies 102 and 103 (Week 48 analysis)

	STRIBILD N=701	**ATRIPLA** N=352	**Atazanavir + ritonavir + TRUVADA** N=355
EYE DISORDERS			
Ocular icterus	<1%	0%	13%
GASTROINTESTINAL DISORDERS			
Diarrhea	12%	11%	16%
Flatulence	2%	<1%	7%
Nausea	16%	9%	13%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue	5%	7%	6%
HEPATOBILIARY DISORDERS			
Jaundice	0%	<1%	8%
NERVOUS SYSTEM DISORDERS			
Somnolence	1%	7%	1%
Headache	7%	4%	6%
Dizziness	3%	20%	4%
PSYCHIATRIC DISORDERS			
Insomnia	3%	8%	1%
Abnormal dreams	9%	26%	3%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Rash[b]	3%	15%	6%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, attributed to study drugs.

b. Rash event includes dermatitis, drug eruption, eczema, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic, and urticaria.

See *Warnings and Precautions (5.3)*, for a discussion of renal adverse events from clinical trials experience with STRIBILD.

Emtricitabine and Tenofovir Disoproxil Fumarate: 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 subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: depression, abdominal pain, dyspepsia, vomiting, fever, pain, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection, arthralgia, back pain, myalgia, paresthesia, peripheral

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neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

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 (Grades 3-4) occurring in at least 2% of subjects receiving STRIBILD in Studies 102 and 103 are presented in Table 3.

Table 3 Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Subjects Receiving STRIBILD in Studies 102 and 103 (Week 48 analysis)

	STRIBILD	ATRIPLA	Atazanavir + ritonavir + TRUVADA
Laboratory Parameter Abnormality	N=701	N=352	N=355
AST (>5.0 x ULN)	2%	3%	4%
Amylase[a] (>2.0 x ULN)	2%	2%	4%
Creatine Kinase (≥ 10.0 x ULN)	5%	11%	7%
Urine RBC (Hematuria) (> 75 RBC/HPF)	3%	1%	2%

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

Proteinuria (all grades) occurred in 39% of subjects receiving STRIBILD, 29% of subjects receiving ATRIPLA, and 24% of subjects receiving atazanavir + ritonavir + TRUVADA.

The cobicistat component of STRIBILD has been shown to increase serum creatinine and decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In Studies 102 and 103, increases in serum creatinine and decreases in estimated creatinine clearance occurred early in treatment with STRIBILD, after which they stabilized. The mean ± SD change in serum creatinine after 48 weeks of treatment was 0.14 mg per dL ± 0.13 mg per dL for STRIBILD, 0.01 mg per dL ± 0.12 mg per dL for ATRIPLA, and 0.09 mg per dL ± 0.13 mg per dL for atazanavir + ritonavir + TRUVADA. The mean ± SD change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.9 ± 14.9 mL per min for STRIBILD, -1.6 ± 16.5 mL per min for ATRIPLA, and -9.3 ± 15.8 mL per min for atazanavir + ritonavir + TRUVADA. Elevation in serum creatinine (all grades) occurred in 7% of subjects receiving STRIBILD, 1% of subjects receiving ATRIPLA, and 4% of subjects receiving atazanavir + ritonavir + TRUVADA.

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Emtricitabine or Tenofovir Disoproxil Fumarate: In addition to the laboratory abnormalities observed with STRIBILD, the following laboratory abnormalities have been previously reported in subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: Grades 3 or 4 laboratory abnormalities of ALT (M: greater than 215 U per L; F: greater than 170 U per L), alkaline phosphatase (greater than 550 U per L), bilirubin (greater than 2.5 x ULN), serum glucose (less than 40 or greater than 250 mg per dL), glycosuria (greater than or equal to 3+), neutrophils (less than 750 per mm^3), fasting cholesterol (greater than 240 mg per dL), and fasting triglycerides (greater than 750 mg per dL).

Serum Lipids: In the clinical trials of STRIBILD, a similar percentage of subjects receiving STRIBILD, ATRIPLA, and atazanavir + ritonavir + TRUVADA were on lipid lowering agents at baseline (11%, 11%, and 12%, respectively). While receiving study drug through Week 48, an additional 4% of STRIBILD subjects were started on lipid lowering agents, compared to 5% of ATRIPLA and 7% of atazanavir + ritonavir + TRUVADA subjects. During the first 48 weeks of study drug exposure, 1% or fewer subjects in any treatment arm experienced Grades 3 or 4 elevations in fasting cholesterol (greater than 300 mg per dL) or fasting triglycerides (greater than 750 mg per dL).

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 4.

Table 4 Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving STRIBILD or Comparator in Studies 102 and 103

	STRIBILD N=701		**ATRIPLA N=352**		**Atazanavir + ritonavir + TRUVADA N=355**	
	Baseline	**Week 48**	**Baseline**	**Week 48**	**Baseline**	**Week 48**
	mg/dL	Change[a]	mg/dL	Change[a]	mg/dL	Change[a]
Total Cholesterol (fasted)	166 [N=675]	+11 [N=606]	161 [N=343]	+19 [N=298]	168 [N=337]	+9 [N=287]
HDL-cholesterol (fasted)	43 [N=675]	+6 [N=605]	43 [N=343]	+8 [N=298]	42 [N=335]	+5 [N=284]
LDL-cholesterol (fasted)	100 [N=675]	+10 [N=606]	97 [N=343]	+17 [N=298]	101 [N=337]	+11 [N=288]
Triglycerides (fasted)	122 [N=675]	+13 [N=606]	121 [N=343]	+13 [N=298]	132 [N=337]	+29 [N=287]

a. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values.

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6.2 Postmarketing Experience

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of tenofovir DF. No additional postmarketing adverse reactions specific for emtricitabine have been identified.

Immune System Disorders

allergic reaction, including angioedema

Metabolism and Nutrition Disorders

lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

dyspnea

Gastrointestinal Disorders

pancreatitis, increased amylase, abdominal pain

Hepatobiliary 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, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

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

General Disorders and Administration Site Conditions

asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

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7 DRUG INTERACTIONS

See also *Contraindications (4)* and *Clinical Pharmacology (12.3).*

STRIBILD is a complete regimen for the treatment of HIV-1 infection; therefore, STRIBILD should not be administered with other antiretroviral medications for treatment of HIV-1 infection. Complete information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

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 administered concurrently with products containing ritonavir or regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

7.1 Potential for STRIBILD to Affect Other Drugs

Cobicistat, a component of STRIBILD, is an inhibitor of CYP3A and CYP2D6. The transporters that cobicistat inhibits include 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 is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

7.2 Potential for Other Drugs to Affect One or More Components of STRIBILD

Elvitegravir and cobicistat, components of STRIBILD, are metabolized by CYP3A. Cobicistat is also metabolized, to a minor extent, by CYP2D6.

Drugs that induce CYP3A activity are expected to increase the clearance of elvitegravir and cobicistat, resulting in decreased plasma concentration of cobicistat and elvitegravir, which may lead to loss of therapeutic effect of STRIBILD and development of resistance (see Table 5).

Coadministration of STRIBILD with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat (see Table 5).

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7.3 Drugs Affecting Renal Function

Because emtricitabine and tenofovir, components of STRIBILD are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of STRIBILD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine, tenofovir, and other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to acyclovir, cidofovir, ganciclovir, valacyclovir, and valganciclovir.

7.4 Established and Other Potentially Significant Interactions

Table 5 provides a listing of established or potentially clinically significant drug-drug interactions. The drug interactions described are based on studies conducted with either STRIBILD, the components of STRIBILD, (elvitegravir, cobicistat, emtricitabine, and tenofovir DF) as individual agents and/or in combination, or are predicted drug interactions that may occur with STRIBILD [for magnitude of interaction, see *Clinical Pharmacology (12.3)*]. The table includes potentially significant interactions but is not all inclusive.

Table 5 Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents: Antacids* (for example aluminum and magnesium hydroxide)	↓ elvitegravir	Elvitegravir plasma concentrations are lower when STRIBILD is administered simultaneously with antacids. It is recommended to separate STRIBILD and antacid administration by at least 2 hours.
Proton Pump Inhibitors H_2 Receptor Antagonists	⇔ elvitegravir	No dose adjustment is needed when STRIBILD is combined with either H_2 receptor antagonists or proton pump inhibitors.
Antiarrhythmics: e.g. amiodarone bepridil digoxin* disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics ↑ digoxin	Concentrations of these antiarrhythmic drugs may be increased when coadministered with STRIBILD. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with STRIBILD.

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Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ cobicistat	Concentrations of clarithromycin and/or cobicistat may be altered when clarithromycin is coadministered with STRIBILD. Patients with CLcr greater than or equal to 60 mL/min: No dose adjustment of clarithromycin is required. Patients with CLcr between 50 mL/min and 60 mL/min: The dose of clarithromycin should be reduced by 50%. Concentrations of telithromycin and/or cobicistat may be increased when telithromycin is coadministered with STRIBILD.
Anticoagulants: warfarin	Effect on warfarin unknown	Concentrations of warfarin may be affected upon coadministration with STRIBILD. It is recommended that the international normalized ratio (INR) be monitored upon coadministration with STRIBILD.
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin clonazepam ethosuximide	↑ carbamazepine ↓ elvitegravir ↓ cobicistat ↑ clonazepam ↑ ethosuximide	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin with STRIBILD 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. Concentrations of clonazepam and ethosuximide may be increased when coadministered with STRIBILD. Clinical monitoring is recommended upon coadministration with STRIBILD.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) e.g. paroxetine Tricyclic Antidepressants (TCAs) e.g. amitriptyline desipramine imipramine nortriptyline buproprion trazodone	↑ SSRIs ↑ TCAs ↑ trazodone	Concentrations of these antidepressant agents may be increased when coadministered with STRIBILD. Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.
Antifungals: itraconazole ketoconazole* voriconazole	↑ elvitegravir ↑ cobicistat ↑ itraconazole ↑ ketoconazole ↑voriconazole	Concentrations of ketoconazole, itraconazole and voriconazole may increase upon coadministration with STRIBILD. When administering with STRIBILD, the maximum daily dose of ketoconazole or itraconazole should not exceed 200 mg per day. An assessment of benefit/risk ratio is recommended to justify use of voriconazole with STRIBILD.

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Anti-gout: colchicine	↑ colchicine	STRIBILD should not be coadministered with colchicine to patients with renal or hepatic impairment. Treatment of gout-flares – coadministration of colchicine in patients receiving STRIBILD: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. Prophylaxis of gout-flares – coadministration of colchicine in patients receiving STRIBILD: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever – coadministration of colchicine in patients receiving STRIBILD: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifabutin* rifapentine	↓ elvitegravir ↓ cobicistat	Coadministration of rifabutin and rifapentine with STRIBILD may significantly decrease elvitegravir and cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of STRIBILD with rifabutin or rifapentine is not recommended.
Beta-Blockers: e.g. metoprolol timolol	↑ beta-blockers	Concentrations of beta-blockers may be increased when coadministered with STRIBILD. Clinical monitoring is recommended and a dose decrease of the beta blocker may be necessary when these agents are coadministered with STRIBILD.
Calcium Channel Blockers: e.g. amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with STRIBILD. Caution is warranted and clinical monitoring is recommended upon coadministration with STRIBILD.
Corticosteroid: **Systemic:** dexamethasone	↓ elvitegravir ↓ cobicistat	Systemic dexamethasone, a CYP3A inducer, may significantly decrease elvitegravir and cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance.
Corticosteroid: **Inhaled/Nasal:** 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.

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Endothelin Receptor Antagonists: bosentan	↑ bosentan	Coadministration of bosentan in patients on STRIBILD: In patients who have been receiving STRIBILD for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Coadministration of STRIBILD in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of STRIBILD. After at least 10 days following the initiation of STRIBILD, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
HMG-CoA Reductase Inhibitors: atorvastatin	↑ atorvastatin	Initiate with the lowest starting dose of atorvastatin and titrate carefully while monitoring for safety.
Hormonal Contraceptives: norgestimate/ethinyl estradiol*	↑ norgestimate ↓ ethinyl estradiol	The effects of increases in the concentration of the progestational component 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 estradiol 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 contraceptives containing progestogens other than norgestimate has not been studied; therefore, alternative (non hormonal) methods of contraception can be considered.
Immuno-suppressants: e.g. cyclosporine sirolimus tacrolimus	↑ immuno-suppressants	Concentrations of these immunosuppressant agents may be increased when coadministered with STRIBILD. Therapeutic monitoring of the immunosuppressive agents is recommended upon coadministration with STRIBILD.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol and STRIBILD is not recommended. Coadministration of salmeterol with STRIBILD may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Neuroleptics: e.g. perphenazine risperidone thioridazine	↑ neuroleptics	A decrease in dose of the neuroleptic may be needed when coadministered with STRIBILD.

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Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	Coadministration with STRIBILD may result in an increase in PDE-5 inhibitor associated adverse events, including hypotension, syncope, visual disturbances, and priapism. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> • Use of sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH). • The following dose adjustments are recommended for the use of tadalafil with STRIBILD: *Coadministration of tadalafil in patients on STRIBILD:* In patients receiving STRIBILD for at least 1 week, start tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. *Coadministration of STRIBILD in patients on tadalafil:* Avoid use of tadalafil during the initiation of STRIBILD. Stop tadalafil at least 24 hours prior to starting STRIBILD. After at least one week following initiation of STRIBILD, resume tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours, or tadalafil at a single dose not exceeding 10 mg in 72 hours can be used with increased monitoring for PDE-5 inhibitor associated with adverse events.
Sedative/hypnotics: Benzodiazepines: e.g. Parenterally administered midazolam clorazepate diazepam estazolam flurazepam buspirone zolpidem	↑ sedatives/hypnotics	Concomitant use of parenteral midazolam with STRIBILD may increase plasma concentrations of midazolam. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with STRIBILD is contraindicated. With other sedative/hypnotics, dose reduction may be necessary and clinical monitoring is recommended.

* Indicates that a drug-drug interaction trial was conducted.

a. This table is not all inclusive.

b. ↑ = Increase, ↓ = Decrease, ⇔ = No Effect

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7.5 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 when STRIBILD is combined with the following drugs: entecavir, famciclovir, and ribavirin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction 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.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to STRIBILD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Animal Data

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 (AUC) 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 daily dose of 150 mg.

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 (AUC) at the embryo-fetal 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.

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area

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comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that elvitegravir, cobicistat, and tenofovir are secreted in milk. It is not known whether elvitegravir or cobicistat is excreted in human milk.

In humans, samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. 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.

Samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk. Tenofovir-associated risks, including the risk of viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving STRIBILD.**

8.4 Pediatric Use

Safety and effectiveness of STRIBILD in pediatric patients less than 18 years of age have not been established *[See Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical studies of STRIBILD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[See Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL per min. Because STRIBILD is a fixed-dose combination tablet, STRIBILD

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should be discontinued if estimated creatinine clearance declines below 50 mL per min during treatment with STRIBILD as dose interval adjustment required for emtricitabine and tenofovir DF cannot be achieved *[See Warnings and Precautions (5.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].*

8.7 Hepatic Impairment

No dose adjustment of STRIBILD is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of STRIBILD in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, STRIBILD is not recommended for use in patients with severe hepatic impairment *[See Dosage and Administration (2) and Clinical Pharmacology (12.3)].*

10 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 as well as observation of the clinical status of the patient.

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, a 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.

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 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis 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 per minute and a dialysate flow rate of 600 mL per minute). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one study, 600 mg tenofovir DF

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was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

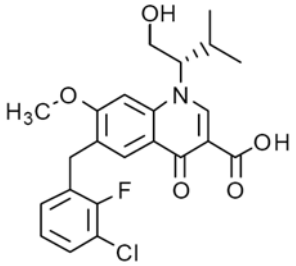
11 DESCRIPTION

STRIBILD is a fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir DF. Elvitegravir is a HIV-1 integrase strand transfer inhibitor. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. Tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. VIREAD is the brand name for tenofovir DF. Emtricitabine is a synthetic nucleoside analog of cytidine. EMTRIVA is the brand name for emtricitabine.

STRIBILD tablets are for oral administration. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil). The tablets include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate. The tablets are film-coated with a coating material containing indigo carmine (FD&C Blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

Elvitegravir: The chemical name of elvitegravir is 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.9. It has the following structural formula:



Elvitegravir is a white to pale yellow powder with a solubility of less than 0.3 micrograms per mL in water at 20 °C.

Cobicistat: The chemical name for cobicistat is 1,3-thiazol-5-ylmethyl [(2*R*,5*R*)-5-{[(2*S*)-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.

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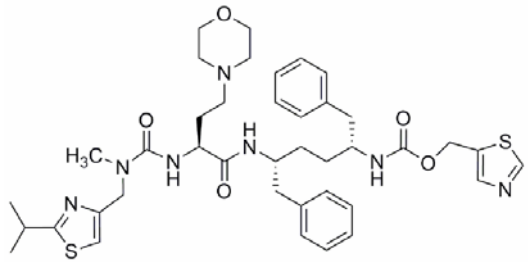
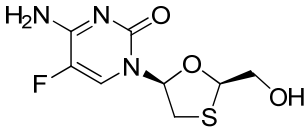
It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0. It has the following structural formula:



Cobicistat is adsorbed onto silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

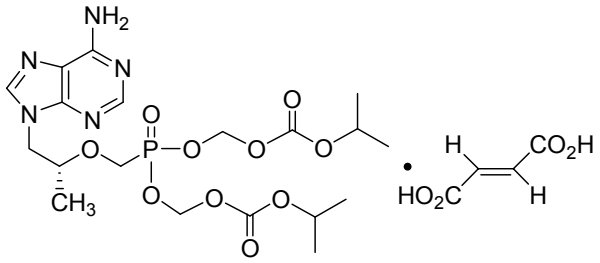
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.25. It has the following structural formula:



Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg per mL in water at 25 °C.

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[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.51. It has the following structural formula:



Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg per mL in water at 25 °C. All dosages are expressed in terms of tenofovir DF except where otherwise noted.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

STRIBILD is a fixed-dose combination of antiviral drugs elvitegravir boosted by the pharmacokinetic enhancer cobicistat, emtricitabine, and tenofovir DF *[See Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram

Thorough QT studies have been conducted for elvitegravir and cobicistat. The effect of the other two components, tenofovir and emtricitabine, or the combination regimen STRIBILD on the QT interval is not known.

The effect of multiple doses of elvitegravir 125 and 250 mg (coadministered with 100 mg ritonavir) on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel group thorough QT study in 126 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 250 mg elvitegravir (with 100 mg ritonavir) is expected to cover the high exposure clinical scenario.

The effect of a single dose of cobicistat 250 mg and 400 mg on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 48 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTc) was below 10 ms, the threshold for regulatory concern. The dose of 400 mg cobicistat is expected to cover the high exposure clinical scenario. Prolongation of the PR interval was noted in subjects receiving cobicistat in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) ms for 250 mg dose and 20.2 (22.8) for 400 mg dose cobicistat. Because the 150 mg cobicistat dose used in the STRIBILD fixed-dose combination tablet is lower than the lowest dose studied in the thorough QT study, it is unlikely that treatment with STRIBILD will result in clinically relevant PR prolongation.

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12.3 Pharmacokinetics

Pharmacokinetics in Adults

Absorption and Bioavailability

STRIBILD: Following oral administration of STRIBILD with food in HIV-1 infected subjects, peak plasma concentrations were observed 4 hours post-dose for elvitegravir, 3 hours post-dose for cobicistat, 3 hours post-dose for emtricitabine, and 2 hours for tenofovir following the rapid conversion of tenofovir DF (see Table 6 for additional pharmacokinetic parameters).

Table 6 Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Exposure Following Oral Administration of STRIBILD in HIV-Infected Subjects

Parameter Mean ± SD [range: min:max]	Elvitegravir[a]	Cobicistat[b]	Emtricitabine[b]	Tenofovir[b]
C_{max} (microgram per mL)	1.7 ± 0. 4 [0.4:3.7]	1.1 ± 0.4 [0.1:2.1]	1.9 ± 0.5 [0.6:3.6]	0.45 ± 0.2 [0.2:1.2]
AUC_{tau} (microgram•hour per mL)	23.0 ± 7.5 [4.4:69.8]	8.3 ± 3.8 [0.5:18.3]	12.7 ± 4.5 [5.2:34.1]	4.4 ± 2.2 [2.1:18.2]
C_{trough} (microgram per mL)	0.45 ± 0.26 [0.05:2.34]	0.05 ± 0.13 [0.01:0.92]	0.14 ± 0.25 [0.04:1.94]	0.10 ± 0.08 [0.04:0.58]

SD = Standard Deviation

a. From Population Pharmacokinetic analysis, N=419.

b. From Intensive Pharmacokinetic analysis, N=61-62, except cobicistat C_{trough} N=53.

Effect of Food on Oral Absorption

Relative to fasting conditions, the administration of single dose STRIBILD with a light meal (~373 kcal, 20% fat) increased the mean systemic exposure of elvitegravir and tenofovir by 34% and 24%, respectively. The alterations in mean systemic exposures of cobicistat and emtricitabine were not clinically significant.

Relative to fasting conditions, the administration of single dose STRIBILD with a high fat meal (~ 800 kcal, 50% fat) increased the mean systemic exposure of elvitegravir and tenofovir by 87% and 23%, respectively. The alterations in mean systemic exposures of cobicistat and emtricitabine were not clinically significant.

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Distribution

Elvitegravir: Elvitegravir is 98-99% bound to human plasma proteins and binding is independent of drug concentration over the range of 1 ng per mL to 1.6 micrograms per mL. The mean blood-to-plasma ratio was 0.73.

Cobicistat: Cobicistat is 97-98% bound to human plasma proteins and the mean blood-to-plasma ratio was approximately 0.5.

Emtricitabine: In vitro binding of emtricitabine to human plasma proteins is less than 4% and is independent of drug concentration over the range of 0.02–200 micrograms per mL.

Tenofovir Disoproxil Fumarate: In vitro binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01–25 micrograms per mL.

Metabolism

Elvitegravir: The majority of elvitegravir metabolism is mediated by CYP3A enzymes. Elvitegravir also undergoes glucuronidation via UGT1A1/3 enzymes.

Cobicistat: Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.

Emtricitabine and tenofovir are not significantly metabolized.

Elimination

Elvitegravir: The median terminal plasma half-life of elvitegravir following administration of STRIBILD is approximately 12.9 hours. After single dose administration of [^{14}C] elvitegravir (coadministered with 100 mg ritonavir), 94.8 % and 6.7 % of the administered dose was excreted in feces and urine, respectively.

Cobicistat: The median terminal plasma half-life of cobicistat following administration of STRIBILD is approximately 3.5 hours. With single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for six days, 86.2 % and 8.2 % of the administered dose was excreted in feces and urine, respectively.

Emtricitabine and tenofovir are primarily excreted in the urine by a combination of glomerular filtration and active tubular secretion.

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Special Populations

Patients with Renal Impairment

Elvitegravir and cobicistat: A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in healthy subjects and subjects with severe renal impairment (estimated creatinine clearance less than 30 mL per min). No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

Emtricitabine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with estimated creatinine clearance below 50 mL per min or with end stage renal disease requiring dialysis, *[See Warnings and Precautions (5.3) and Use in Specific Populations (8.6)].*

Patients with Hepatic Impairment

Elvitegravir and cobicistat: A study of the pharmacokinetics of cobicistat-boosted elvitegravir was performed in healthy subjects and subjects with moderate hepatic impairment. No clinically relevant differences in elvitegravir or cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) 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 (Child-Pugh Class C) on the pharmacokinetics of elvitegravir or cobicistat has not been studied *[See Use in Specific Populations (8.7)].*

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

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD has been studied in healthy subjects with moderate to severe hepatic impairment. No clinically relevant differences in tenofovir pharmacokinetics were observed between subjects with hepatic impairment and healthy subjects.

Hepatitis B and/or Hepatitis C Virus Co-infection

Elvitegravir: 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 cobicistat boosted elvitegravir.

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Cobicistat: There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of cobicistat.

Emtricitabine and Tenofovir: Pharmacokinetics of emtricitabine and tenofovir DF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Race

Elvitegravir: Population pharmacokinetic analysis of elvitegravir in HIV-1 infected subjects indicated that race had no clinically relevant effect on the exposure of cobicistat-boosted elvitegravir.

Cobicistat: There were insufficient pharmacokinetic data in the clinical trials to determine the effect of race on the pharmacokinetics of cobicistat.

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of EMTRIVA.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of VIREAD.

Gender

No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat-boosted elvitegravir, emtricitabine and tenofovir DF. There was insufficient pharmacokinetic data in clinical trials to determine the effect of gender on the pharmacokinetics of cobicistat.

Pediatric Patients

Emtricitabine has been studied in pediatric subjects from 3 months to 17 years of age. Tenofovir DF has been studied in pediatric subjects from 2 years to less than 18 years of age. The pharmacokinetics of elvitegravir or cobicistat in pediatric subjects have not been established *[See Use in Specific Populations (8.4)].*

Geriatric Patients

Pharmacokinetics of elvitegravir, cobicistat, emtricitabine and tenofovir have not been fully evaluated in elderly (65 years of age and older) patients *[See Use in Specific Populations (8.5)].*

Assessment of Drug Interactions

[See also *Contraindications (4)* and *Drug Interactions (7)*]

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The drug-drug interaction studies described in Tables 7 and 8 were conducted with STRIBILD, elvitegravir (coadministered with cobicistat or ritonavir), or cobicistat administered alone.

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 Warnings and Precautions (5.4)].*

The effects of coadministered drugs on the exposure of elvitegravir are shown in Table 7. The effects of elvitegravir or cobicistat on the exposure of coadministered drugs are shown in Table 8. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Antacids	20 mL single dose given 4 hours before elvitegravir	50 single dose	Ritonavir 100 single dose	8	0.95 (0.84,1.07)	0.96 (0.88,1.04)	1.04 (0.93,1.17)
	20 mL single dose given 4 hours after elvitegravir			10	0.98 (0.88,1.10)	0.98 (0.91,1.06)	1.00 (0.90,1.11)
	20 mL single dose given 2 hours before elvitegravir			11	0.82 (0.74,0.91)	0.85 (0.79,0.91)	0.90 (0.82,0.99)
	20 mL single dose given 2 hours after elvitegravir			10	0.79 (0.71,0.88)	0.80 (0.75,0.86)	0.80 (0.73,0.89)
Famotidine	40 once daily given 12 hours after elvitegravir	150 once daily	Cobicistat 150 once daily	10	1.02 (0.89,1.17)	1.03 (0.95,1.13)	1.18 (1.05,1.32)
	40 once daily given simultaneously with elvitegravir			16	1.00 (0.92,1.10)	1.03 (0.98,1.08)	1.07 (0.98,1.17)

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Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	Mean Ratio of Elvitegravir Pharmacokinetic Parameters (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Ketoconazole	200 twice daily	150 once daily	Ritonavir 100 once daily	18	1.17 (1.04,1.33)	1.48 (1.36,1.62)	1.67 (1.48,1.88)
Omeprazole	40 once daily given 2 hours before elvitegravir	50 once daily	Ritonavir 100 once daily	9	0.93 (0.83,1.04)	0.99 (0.91,1.07)	0.94 (0.85,1.04)
	20 once daily given 2 hours before elvitegravir	150 once daily	Cobicistat 150 once daily	11	1.16 (1.04,1.30)	1.10 (1.02,1.19)	1.13 (0.96,1.34)
	20 once daily given 12 hours after elvitegravir			11	1.03 (0.92,1.15)	1.05 (0.93,1.18)	1.10 (0.92,1.32)
Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	0.91 (0.84,0.99)	0.79 (0.74,0.85)	0.33 (0.27,0.40)
Rosuvastatin	10 single dose	150 once daily	Cobicistat 150 once daily	10	0.94 (0.83,1.07)	1.02 (0.91,1.14)	0.98 (0.83,1.16)

a. All interaction studies conducted in healthy volunteers.

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Elvitegravir, Elvitegravir plus Cobicistat, Cobicistat, or STRIBILD[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Elvitegravir Dose[b] (mg)	Cobicistat or Ritonavir Booster Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters[c] (90% CI); No effect = 1.00		
					C_{max}	AUC	C_{min}
Desipramine	50 single dose	N/A	Cobicistat 150 once daily	8	1.24 (1.08,1.44)	1.65 (1.36,2.02)	NC
Digoxin	0.5 single dose	N/A	Cobicistat 150 once daily	22	1.41 (1.29,1.55)	1.08 (1.00, 1.17)	NC
Norgestimate/ ethinyl estradiol	0.180/0.215/ 0.250 norgestimate once daily	150 once daily[d]	Cobicistat 150 once daily[d]	13	2.08 (2.00,2.17)	2.26 (2.15,2.37)	2.67 (2.43,2.92)
	0.025 ethinyl estradiol once daily				0.94 (0.86,1.04)	0.75 (0.69,0.81)	0.56 (0.52,0.61)

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Rifabutin	150 once every other day	150 once daily	Cobicistat 150 once daily	12	1.09 (0.98,1.20)[e]	0.92 (0.83,1.03)[e]	0.94 (0.85,1.04)[e]
25-O-desacetyl-rifabutin				12	4.84 (4.09,5.74)[e]	6.25 (5.08,7.69)[e]	4.94 (4.04,6.04)[e]
Rosuvastatin	10 single dose	150 single dose	Cobicistat 150 single dose	10	1.89 (1.48,2.42)	1.38 (1.14,1.67)	NC

a. All interaction studies conducted in healthy volunteers.
b. N/A = Not Applicable
c. NC = Not Calculated
d. Study conducted with STRIBILD.
e. Comparison based on rifabutin 300 mg once daily.

12.4 Microbiology

Mechanism of Action

Elvitegravir: Elvitegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), 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. 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.

Emtricitabine: Emtricitabine, a synthetic nucleoside analog 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 and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ.

Tenofovir Disoproxil Fumarate: Tenofovir DF is an acyclic nucleoside phosphonate diester analog 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 DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

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Antiviral Activity in Cell Culture

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate: The triple combination of elvitegravir, emtricitabine, and tenofovir was not antagonistic in cell culture combination antiviral activity assays and was not affected by the addition of cobicistat.

Elvitegravir: The antiviral activity of elvitegravir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, monocyte/macrophage cells, and primary peripheral blood lymphocytes. The 50% effective concentrations (EC_{50}) ranged from 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_{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC_{50} value of 0.53 nM). The antiviral activity of elvitegravir with antiretroviral drugs in two-drug combination studies was not antagonistic when combined with the INSTI raltegravir, NNRTIs (efavirenz, etravirine, or nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine), PIs (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir), the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist maraviroc. Elvitegravir did not show inhibition of replication of HBV or HCV in cell culture.

Cobicistat: Cobicistat has no detectable antiviral activity in cell culture against HIV-1, HBV, or HCV and does not antagonize the antiviral activity of elvitegravir, emtricitabine, or tenofovir.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for emtricitabine were in the range of 0.0013–0.64 micromolar. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 micromolar) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 micromolar). No antagonistic effects were observed in two-drug combination studies of emtricitabine with NRTIs (abacavir, lamivudine, stavudine, tenofovir, or zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, or rilpivirine), PIs (amprenavir, nelfinavir, ritonavir, or saquinavir), or the INSTI elvitegravir.

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 micromolar. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 micromolar) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6–5.5 micromolar). No antagonistic effects were observed in two-drug combination studies of tenofovir with NRTIs (abacavir, didanosine, emtricitabine,

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lamivudine, stavudine, or zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, or rilpivirine), PIs (amprenavir, indinavir, nelfinavir, ritonavir, or saquinavir), or the INSTI elvitegravir.

Resistance

In Cell Culture:

Elvitegravir: HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R. Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M.

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to emtricitabine or tenofovir have been selected in cell culture. Reduced susceptibility to emtricitabine was associated with M184V/I substitutions in HIV-1 RT. HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

In Treatment-Naïve HIV-1-Infected Subjects:

Virus samples from STRIBILD-treatment failure subjects in Studies 102 and 103 who were viremic with HIV-1 RNA greater than 400 copies per mL at virologic failure, at Week 48, or at the time of early study drug discontinuation were evaluated for STRIBILD resistance (genotypic and phenotypic data available for 23 subjects [3%, 23/669]). The development of one or more primary substitutions associated with resistance to elvitegravir, emtricitabine, and/or tenofovir was observed in 57% (13/23) of the viremic subjects with evaluable genotypic data. The most common substitutions that emerged were M184V/I (N=12) in HIV-1 RT and the primary elvitegravir resistance-associated substitutions T66I (N=2), E92Q (N=8), Q148R (N=3), and N155H (N=3) in integrase; K65R in RT was also detected (N=4). In isolates with primary elvitegravir resistance substitutions, additional substitutions in integrase associated with resistance to elvitegravir were H51Y, L68I/V, G140C, S153A, E157Q, V165I, and H183P. Failure isolates expressing primary elvitegravir resistance-associated substitutions (N=11) had median decreases in susceptibility to elvitegravir of 44-fold (range: 6- to greater than 198-fold) and 33-fold (range: 4- to greater than 122-fold) compared to wild-type reference HIV-1 and to the respective baseline isolates, respectively. Most subjects (N=10) who developed integrase substitutions associated with elvitegravir resistance also developed the M184I/V RT substitutions, conferring reduced susceptibility to both elvitegravir and emtricitabine. In phenotypic analyses, 50% (11/22) of the viremic subjects with evaluable data had HIV-1 isolates with reduced susceptibility to elvitegravir, 57% (12/21) had reduced susceptibility to emtricitabine, and 10% (2/21) had reduced susceptibility to tenofovir.

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Cross Resistance

STRIBILD-treatment failure subject isolates exhibited varying degrees of cross resistance within the INSTI and NRTI drug classes depending on the specific substitutions observed. These isolates remained susceptible to all NNRTIs and protease inhibitors.

Elvitegravir: Cross-resistance has been observed among INSTIs. Elvitegravir-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir depending on the type and number of substitutions in HIV-1 integrase. Among the four primary elvitegravir resistance-associated substitutions detected in the STRIBILD-treatment virologic failure isolates, E92Q, Q148R, and N155H individually conferred reduced susceptibility both to elvitegravir (greater than 32-fold) and raltegravir (greater than 5-fold) when introduced into a wild-type virus by site-directed mutagenesis. The T66I substitution conferred greater than 14-fold reduced susceptibility to elvitegravir but less than 3-fold to raltegravir. Among the three primary raltegravir resistance-associated substitutions (Y143H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred significant reductions in susceptibility to elvitegravir (greater than 5-fold).

Emtricitabine: Cross-resistance has been observed among NRTIs. Emtricitabine-resistant isolates harboring an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by emtricitabine.

Tenofovir Disoproxil Fumarate: Cross-resistance has been observed among NRTIs. The K65R substitution in HIV-1 RT selected by tenofovir is also selected in some HIV-1-infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R substitution. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V RT substitution without zidovudine resistance-associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4) in HIV-1 RT, all of whom had a reduced response in clinical trials.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Elvitegravir: Long-term carcinogenicity studies of elvitegravir were carried out in mice (104 weeks) and in rats for up to 88 weeks (males) and 90 weeks (females). No drug-related increases in tumor incidence were found in mice at doses up to 2000 mg per kg per day alone or in combination with 25 mg per kg per day ritonavir at exposures 3- and 14-fold, respectively, the human systemic exposure at the recommended daily dose of 150 mg. No drug-related increases in tumor incidence were found in rats at doses up to 2000 mg per kg per day at exposures 12- to 27-fold, respectively in male and female, the human systemic exposure.

Elvitegravir was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an *in vitro* chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at 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: The assessment of the carcinogenicity studies of cobicistat is ongoing.

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

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-fold higher than human exposures at the recommended 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.

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the therapeutic dose of 200 mg per day) or

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in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the therapeutic dose).

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

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir DF 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 therapeutic dose for HIV 1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times of 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.

Tenofovir DF was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

14 CLINICAL STUDIES

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

In Study 102, subjects were randomized in a 1:1 ratio to receive either STRIBILD (N=348) once daily or ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg; N=352) once daily. The mean age was 38 years (range 18-67), 89% were male, 63% were White, 28% were Black, and 2% were Asian. Twenty-four percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies per mL (range 2.6–6.5). The mean baseline CD4+ cell count was 386 cells per mm^3 (range 3-1348) and 13% had CD4+ cell counts less than 200 cells

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per mm^3. Thirty-three percent of subjects had baseline viral loads greater than 100,000 copies per mL.

In Study 103, subjects were randomized in a 1:1 ratio to receive either STRIBILD (N=353) once daily or atazanavir 300 mg + ritonavir 100 mg (ATV+RTV) + TRUVADA (emtricitabine 200 mg/tenofovir DF 300 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. Sixteen percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.8 log_{10} copies per mL (range 1.7-6.6). The mean baseline CD4+ cell count was 370 cells per mm^3 (range 5-1132) and 13% had CD4+ cell count less than 200 cells per mm^3. Forty-one percent of subjects had baseline viral loads greater than 100,000 copies per mL.

In both studies, subjects were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL or greater than 100,000 copies per mL).

Treatment outcomes of Study 102 and Study 103 through 48 weeks are presented in Table 9.

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Table 9 Virologic Outcome of Randomized Treatment of Study 102 and Study 103 at Week 48[a]

	Study 102		Study 103	
	STRIBILD (N=348)	**ATRIPLA (N=352)**	**STRIBILD (N=353)**	**ATV + RTV + TRUVADA (N=355)**
Virologic Success 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%)	
Virologic Failure[b]	7%	7%	5%	5%
No Virologic Data at Week 48 Window				
Discontinued Study Drug Due to AE or Death[c]	3%	5 %	3%	5%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	2%	3%	2%	3%
Missing Data During Window but on Study Drug	0%	<1 %	0%	< 1 %

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

b. Includes subjects who had ≥50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

c. 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.

d. Includes subjects 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.

In Study 102, the mean increase from baseline in CD4+ cell count at Week 48 was 230 cells per mm^3 in the STRIBILD-treated subjects and 193 cells per mm^3 in the ATRIPLA-treated subjects. In Study 103, the mean increase from baseline in CD4+ cell count at Week 48 was 202 cells per mm^3 in the STRIBILD-treated subjects and 201 cells per mm^3 in the atazanavir + ritonavir + TRUVADA-treated subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

STRIBILD tablets are green, capsule-shaped, film-coated, debossed with “GSI” on one side and the number “1” surrounded by a square box (1) on the other side. Each bottle contains 30 tablets (NDC 61958-1201-1), a silica gel desiccant and closed with a child-resistant closure.

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

- Keep container tightly closed.
- Dispense only in original container.

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- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

- *See FDA-Approved Patient Labeling (Patient Information)*

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with STRIBILD.** A Patient Package Insert for STRIBILD is available for patient information.

Information for Patients

Patients should be advised that:

- STRIBILD may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort.
- Patients should remain under the care of a healthcare provider when using STRIBILD.
- Patients should be informed that STRIBILD is not a cure for HIV-1 infection. Patients should stay on continuous HIV therapy to control HIV-1 infection and decrease HIV-related illnesses. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.
- Patients should avoid doing things that can spread HIV-1 infection to others.
    - **Do not share needles or other injection equipment.**
    - **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
    - **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
    - **Do not breastfeed.** At least two of the drugs contained in STRIBILD can be passed to the baby in breast milk. It is not known whether this could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.
    - It is important to take STRIBILD on a regular dosing schedule with food and to avoid missing doses.
    - Do not miss a dose of STRIBILD. If a patient misses a dose of STRIBILD, the patient should take the missed dose as soon as they remember. If it is almost time for the next dose of STRIBILD, the patient should not take the missed dose, but resume the usual dosing schedule. Inform the patient that he or she should not take more or less than the prescribed dose of STRIBILD at any one time.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with STRIBILD should be suspended in any patients who

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develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.

- Patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD *[See Warnings and Precautions (5.2)]*. STRIBILD should not be discontinued without first informing their healthcare provider.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of STRIBILD. STRIBILD should be avoided with concurrent or recent use of a nephrotoxic agent *[See Warnings and Precautions (5.3)]*.
- STRIBILD should not be coadministered with other antiretroviral products because it provides a complete treatment regimen and because of potential drug interactions *[See Warnings and Precautions (5.4) and Drug Interactions (7)]*.
- STRIBILD should not be administered in combination with ATRIPLA, COMPLERA, EMTRIVA, TRUVADA, or VIREAD; with drugs containing lamivudine, including COMBIVIR, EPIVIR or EPIVIR-HBV, EPZICOM, or TRIZIVIR; with drugs containing ritonavir or regimens containing ritonavir; or with HEPSERA *[See Warnings and Precautions (5.4)]*.
- Decreases in bone mineral density have been observed with the use of STRIBILD. Assessment of bone mineral density (BMD) should be considered in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss *[See Warnings and Precautions (5.5)]*.
- Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known *[See Warnings and Precautions (5.6)]*.
- In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Patients should be advised to inform their healthcare provider immediately of any symptoms of infection *[See Warnings and Precautions (5.7)].*

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Patient Information

STRIBILD™ (STRY-bild)
(elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate)
Tablets

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with STRIBILD. For more information, see the section "What should I tell my healthcare provider before taking STRIBILD?"

Read this Patient Information before you start taking STRIBILD and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about STRIBILD?

STRIBILD can cause serious side effects, including:

1. **Build-up of lactic acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take STRIBILD or similar (nucleoside analogs) medicines. Lactic acidosis is a serious medical emergency that can lead to death.

   Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms which could be signs of lactic acidosis:**

   - feel very weak or tired
   - have unusual (not normal) muscle pain
   - have trouble breathing
   - have stomach pain with
     - nausea
     - vomiting
   - feel cold, especially in your arms and legs
   - feel dizzy or lightheaded
   - have a fast or irregular heartbeat

2. **Severe liver problems.** Severe liver problems can happen in people who take STRIBILD. In some cases, these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

   Call your healthcare provider right away if you get any of the following symptoms of liver problems:

   - your skin or the white part of your eyes turns yellow (jaundice)
   - dark "tea-colored" urine
   - light-colored bowel movements (stools)
   - loss of appetite for several days or longer
   - nausea

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- stomach pain

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking STRIBILD for a long time.

3. **Worsening of Hepatitis B infection. If you have hepatitis B virus (HBV) infection and take STRIBILD, your HBV may get worse (flare-up) if you stop taking STRIBILD. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
   - Do not run out of STRIBILD. Refill your prescription or talk to your healthcare provider before your STRIBILD is all gone.
   - Do not stop taking STRIBILD without first talking to your healthcare provider.
   - If you stop taking STRIBILD, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking STRIBILD.

For more information about side effects, see the section **"What are the possible side effects of STRIBILD?"**

What is STRIBILD?

STRIBILD is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults who have never taken HIV-1 medicines before. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

STRIBILD contains the prescription medicines elvitegravir, cobicistat, emtricitabine (EMTRIVA®) and tenofovir disoproxil fumarate (VIREAD®).

It is not known if STRIBILD is safe and effective in children under 18 years of age.

When used to treat HIV-1 infection, STRIBILD may:

- Reduce the amount of HIV-1 in your blood. This is called "viral load".
- Increase the number of CD4+ (T) cells in your blood that help fight off other infections.
- Reduce the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

STRIBILD does not cure HIV-1 infections or AIDS. You must stay on continuous HIV-1 therapy to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

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- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV-1 to other people.

Who should not take STRIBILD?

Do not take STRIBILD if you also take a medicine that contains:

- alfuzosin hydrochloride (UROXATRAL®)
- cisapride (PROPULSID®, PROPULSID QUICKSOLV®)
- ergot-containing medicines, including:
  - dihydroergotamine mesylate (D.H.E. 45®, MIGRANAL®)
  - ergotamine tartrate (CAFERGOT®, MIGERGOT®,ERGOSTAT®, MEDIHALER ERGOTAMINE®, WIGRAINE®, WIGRETTES®)
  - methylergonovine maleate (ERGOTRATE®, METHERGINE®)
- lovastatin (ADVICOR®, ALTOPREV®, MEVACOR®)
- oral midazolam
- pimozide (ORAP®)
- rifampin (RIFADIN®, RIFAMATE®, RIFATER®, RIMACTANE®)
- sildenafil (REVATIO®), when used for treating the lung problem, pulmonary arterial hypertension (PAH)
- simvastatin (SIMCOR®, VYTORIN®, ZOCOR®)
- triazolam (HALCION®)
- St. John's wort (*Hypericum perforatum*) or a product that contains St. John's wort

What should I tell my healthcare provider before taking STRIBILD?

Before taking STRIBILD, tell your healthcare provider if you:

- have liver problems including hepatitis B infection
- have kidney problems
- have bone problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if STRIBILD can harm your unborn baby. Tell your healthcare provider if you become pregnant while taking STRIBILD.

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Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Do not breastfeed if you take STRIBILD.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - Two of the medicines in STRIBILD can pass to your baby in your breast milk. It is not known if the other medicines in STRIBILD can pass into your breast milk.

Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. STRIBILD may affect the way other medicines work, and other medicines may affect how STRIBILD works.

You should not take STRIBILD if you also take:

- any other medicines to treat HIV-1 infection
- other medicines that contain tenofovir (ATRIPLA®, COMPLERA®, VIREAD®, TRUVADA®)
- other medicines that contain emtricitabine or lamivudine (COMBIVIR®, EMTRIVA®, EPIVIR® or EPIVIR-HBV®, EPZICOM®, TRIZIVIR®)
- adefovir (HEPSERA®)

Especially tell your healthcare provider if you take:

- hormone-based contraceptives (birth control pills and patches)
- an antacid medicine that contains aluminum, magnesium hydroxide, or calcium carbonate. Take antacids at least 2 hours before or after you take STRIBILD.
- medicines to treat depression
- medicines to prevent organ transplant rejection
- medicines to treat high blood pressure
- any of the following medicines:
  - amiodarone (CORDARONE®, PACERONE®)
  - atorvastatin (LIPITOR®, CADUET®)
  - bepridil hydrochloric (VASCOR®, BEPADIN®)
  - bosentan (TRACLEER®)
  - buspirone
  - carbamazepine (CARBATROL®, EPITOL®, EQUETRO®, TEGRETO®)
  - clarithromycin (BIAXIN®, PREVPAC®)
  - clonazepam (KLONOPIN®)

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- clorazepate (GEN-XENE®, TRANXENE®)
- colchicine (Colcrys®)
- medicines that contain dexamethasone
- diazepam (VALIUM®)
- digoxin (LANOXIN®)
- disopyramide (NORPACE®)
- estazolam
- ethosuximide (ZARONTIN®)
- flecainide (TAMBOCOR®)
- flurazepam
- fluticasone (FLOVENT®, FLONASE®, FLOVENT® DISKUS, FLOVENT® HFA, VERAMYST®)
- itraconazole (SPORANOX®)
- ketoconazole (NIZORAL®)
- lidocaine (XYLOCAINE®)
- mexiletine
- oxcarbazepine (TRILEPTAL®)
- perphenazine
- phenobarbital (LUMINAL®)
- phenytoin (DILANTIN®, PHENYTEK®)
- propafenone (RYTHMOL®)
- quinidine (NEUDEXTA®)
- rifabutin (MYCOBUTIN®)
- rifapentine (PRIFTIN®)
- risperidone (RISPERDAL®, RISPERDAL CONSTA®)
- salmeterol (SEREVENT®) or salmeterol when taken in combination with fluticasone (ADVAIR DISKUS®, ADVAIR HFA®)
- sildenafil (VIAGRA®), tadalafil (CIALIS®) or vardenafil (LEVITRA®, STAXYN®), for the treatment of erectile dysfunction (ED). If you get dizzy or faint (low blood pressure), have vision changes or have an erection that last longer than 4 hours, call your healthcare provider or get medical help right away.
- tadalafil (ADCIRCA®), for the treatment of pulmonary arterial hypertension
- telithromycin (KETEK®)
- thioridazine
- voriconazole (VFEND®)
- warfarin (COUMADIN®, JANTOVEN®)
- zolpidem (AMBIEN®, EDLULAR®, INTERMEZZO®, ZOLPIMIST®)

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one that is listed above. Do not start any new medicines while you are taking STRIBILD without first talking with your healthcare provider or pharmacist.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take STRIBILD?

- Take STRIBILD exactly as your healthcare provider tells you to take it. **STRIBILD is taken by itself (not with other antiretroviral medicines) to treat HIV-1 infection.**

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- STRIBILD is usually taken 1 time each day.
- Take STRIBILD with food.
- Do not change your dose or stop taking STRIBILD without first talking with your healthcare provider. Stay under a healthcare provider's care when taking STRIBILD.
- Do not miss a dose of STRIBILD. If you miss a dose of STRIBILD, take the missed dose as soon as you remember. If it is almost time for your next dose of STRIBILD, do not take the missed dose. Take the next dose of STRIBILD at your regular time. Do not take 2 doses at the same time to make up for a missed dose.
- If you take too much STRIBILD, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your STRIBILD supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to STRIBILD and become harder to treat.

What are the possible side effects of STRIBILD?

STRIBILD may cause the following serious side effects, including:

- **See "What is the most important information I should know about STRIBILD?"**
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while you are taking STRIBILD. Your healthcare provider may tell you to stop taking STRIBILD if you develop new or worse kidney problems.
- **Bone problems** can happen in some people who take STRIBILD. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do tests to check your bones.
- **Changes in body fat can happen in people who take HIV-1 medicine**. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.

The most common side effects of STRIBILD include:

- nausea
- diarrhea

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Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of STRIBILD. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store STRIBILD?

- Store STRIBILD at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep STRIBILD in its original container.
- Keep the container tightly closed.
- Do not use STRIBILD if the seal over the bottle opening is broken or missing.

Keep STRIBILD and all medicines out of reach of children.

General information about STRIBILD.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use STRIBILD for a condition for which it was not prescribed. Do not give STRIBILD to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about STRIBILD. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about STRIBILD that is written for health professionals.

For more information, call 1-800-445-3235 or go to www.STRIBILD.com.

What are the ingredients in STRIBILD?

Active ingredients: elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate. The tablets are film-coated with a coating material containing indigo carmine (FD&C blue #2) aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

Issued: August 2012

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